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September 1961

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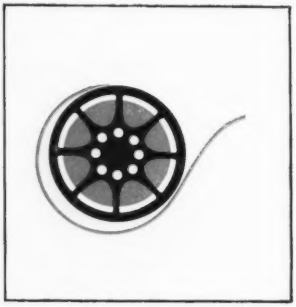

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CONSULTANT welcomes questions and comments about any of the topics covered. The authors will answer all questions by mail, and some of the most informative replies will be published in this section (names will be withheld on request). Please address all correspondence to CONSULTANT, SK&F Laboratories, 1500 Spring Garden Street, Philadelphia 1, Pa.

More About Vasectomy

(Consultant, August '61)

Sir:

After resecting several thousand vas, I feel qualified to comment on (the letter to the Editor about) fatherhood after vasectomy.

One important point to discuss that was not clear was the recanalization following a vasectomy in which a portion of the vas had been removed. I believe a vasectomy can be successful if enough of the vas is resected, i.e., one inch with each end ligated. There have been no failures in my cases using this procedure.

The following point also should be commented on. Some physicians believe that it is possible for the vas "to open up again temporarily" a year or two following a resection of the vas. A test six weeks after the patient's surgery revealed no sperm cells. One and a half years later the wife became pregnant. A semen recheck was negative at that time and has remained so, although the family physician still is of the belief that the husband could be the father even though no positive fertility test could be demonstrated.

In my opinion if the vas ever spontaneously anastomosed for enough sperm to pass through for conception, then it should be that sperm cells would thereafter be found in the semen. Would appreciate further views on these points. Has there ever been an authenticated case of a third vas lying hidden and dormant only to resume its normal function after a bilateral vasectomy had been performed?

I know of several cases in which the wife of a vasectomy patient admitted infidelity to me following confirmation of the pregnancy and begged me to save her family marriage by telling the husband that he was fertile again.

One ingenious wife offered to save a semen sample of her fertile amour, and switch the one of her husband so that he could see for himself "the little things wiggling around in there" when he brought a semen sample in for a check. How many doctors have been fooled into reaching false conclusions regarding the reliability of a properly done vasectomy when wives will devise such cunning schemes to deceive not only their husbands but the medical profession itself?

– Eugene P. Mathias, D.O.
Los Angeles

Repairing Simple Lacerations

(Consultant, July '61)

Dear Doctor Metzger:

Please send the more detailed list of the suggested set (of instruments for repairing lacerations) and its source of supply. Also, any comment regarding the use of fine nylon or dacron white sutures buried permanently?

– R. G. Seibly, M.D.
Bakersfield, California

I have no experience with the subcutaneous permanent use of either of these materials but, as you know, nylon is a stretchy material and would not appear to me to have any particular advantage over conventional suture materials in this regard. Dacron is, of course, a definite possibility, although I doubt that it would have any better physical properties than conventional materials.

– James T. Metzger, M.D.

Dear Doctor Metzger:

Is morphine the drug of choice in small children for laceration preps? (Assuming no brain damage, of course, or respiratory embarrassment.) I would very much like to get away from the "hold-and-holler" method which I now use.

– William C. Douglass, M.D.
Ojai, California

I certainly agree with you that anything we can do to relieve the "hold-and-holler" method of suturing simple lacerations would be most gratifying to patient, family and surgeon.

There has been a general reluctance to use morphine in infants and children, although there is no pharmacologic basis for not doing so. I would say, however, as a matter of practicality that it would probably be better to use Demerol inasmuch as the actual measurement of the dose is easier and therefore less likely to be miscalculated. It is perfectly safe to use five milligrams of Demerol in a newborn infant and to gradually raise the dose from there on.

– James T. Metzger, M.D.

ALLERGY

Paul P. VanArsdel, Jr., M.D.
University of Washington

Paul P. VanArsdel, Jr., is Assistant Professor of Medicine and Head of the Division of Allergy, University of Washington School of Medicine. He received his medical training at the Columbia University College of Physicians and Surgeons. Dr. VanArsdel has published 25 papers in the fields of endocrinology, thyroid physiology, histamine metabolism, immunology, and allergy. His professional affiliations include the American Academy of Allergy and the American College of Physicians. He is Secretary-Treasurer of the Washington State Allergy Society.

WHEN IS ASTHMA ALLERGIC?

Asthma can no longer be considered a specific diagnosis. It is merely a manifestation of a disease in which diffuse obstruction to expiratory breathing produces bothersome symptoms. The causes are specific only on occasion. More often, they are multiple; most often, they are simply not known.

When the pathogenesis of any disease is complex or unknown, it is tempting for one to become a diagnostic "splitter" rather than a "lumper". If I were to yield completely to this temptation, I would end up discussing eight or nine different forms of diffuse obstructive lung disease. Instead, I will discuss three main groups because they offer the greatest challenge to differential diagnosis and treatment. These are atopic asthma, non-atopic asthma, and chronic obstructive pulmonary emphysema. All three have one feature in common; they are diffuse pulmonary diseases with obstruction to expiratory air flow. This obstruction occurs because of varying combinations of bronchospasm, mucosal edema, intra-alveolar secretions, interstitial inflammation, basement membrane thickening, vasodilation and fibrosis. The relative proportion of each varies with pathogenesis and influences the response to therapy. Emphysema itself, due to air trapped in alveoli behind the bronchiolar obstruction, is of secondary importance and is serious only in advanced disease, when the inadequate mixing of alveolar gases during respiration contributes to hypoxia.

Proper classification of asthma requires the use of relatively simple

clinical and laboratory clues that are often overlooked. Tests should be performed to check for the presence of eosinophilia and to get a quantitative recording of the expiratory flow rate. Skin tests should also be made to detect specific allergic sensitivities. In asthma, the antigens to test for are pollens, mold spores, animal danders, feathers, house dust, and other agents that are likely to be inhaled.

In the next few paragraphs, I will give a brief description of each of the three broad types of obstructive lung disease, pointing out confusing similarities, diagnostic differences, and other points that may be helpful in differentiating them.

Atopic Asthma

Atopic asthma is characterized by the hereditary tendency to develop circulating skin-sensitizing antibodies to foreign substances that are generally innocuous to man. Atopic patients manifest their allergy by such disorders as infantile eczema, colic, drug anaphylaxis, hay fever, and asthma. Most have some difficulty before the age of 30. Atopic asthma is paroxysmal; the severity of the attacks depends on the amount of inhaled allergens. Moderate eosinophilia—from 400 to 1000 cells/cu. mm.—is found during symptomatic periods. The vital capacity is low with a slow expiratory flow rate. In uncomplicated atopic asthma, it may return to normal within minutes after administration of epinephrine subcutaneously or use of a nebulized bronchodilator. Skin testing usually produces strong whealing reactions. These tests should be done cautiously, starting with scratch tests or intradermal tests using weak solutions. Asthma that appears in the spring or early summer is most likely caused by pollens. If the asthma is worse in late summer and early fall, weed pollen or mold spore sensitivity should be suspected. Winter asthma is likely to be associated with household allergens such as dust or feathers. A dusty or musty home may be seriously disabling to the atopic asthmatic.

Non-atopic Asthma

Non-atopic asthma, sometimes referred to as intrinsic asthma, is often confused with allergic asthma. Characteristically, it starts after the age of 30 in a person with no personal or familial allergic history. Non-atopic asthma is often associated with chronic infection, particularly of the paranasal sinuses. Patients with this disorder may have nasal or sinus polyps and some have an unusual sensitivity to aspirin. Eosinophils are often present in large numbers, generally more than in uncomplicated atopic asthma. The vital capacity and flow rate are affected as in atopic asthma, but impairment is more pronounced. Improvement with bronchodilators is usually incomplete. Only with adrenocortical steroid therapy will the vital capacity and flow rate approach normal again. Except for occasional moderate reactions to house dust, skin tests are negative. Although bacterial allergy is often suspected in these patients, I have found that skin tests for such antigens are unreliable and proof of bacterial allergy is difficult to get.

Obstructive Pulmonary Emphysema

Obstructive pulmonary emphysema, called chronic bronchitis in Great Britain, has a natural history quite different from asthma, but it is often confused with asthma. It rarely be-

comes symptomatic before the age of 40. While there is no allergic history, this condition may be preceded by several years of chronic cough or recurrent respiratory infections. These patients usually have a history of heavy cigarette smoking or prolonged exposure to industrial air pollution. Usually gradually and relentlessly progressive with no asymptomatic periods, it often gets much worse when the patient picks up a minor respiratory infection. There is no blood eosinophilia. The vital capacity is low and the ventilatory flow rate is often very slow. In contrast to the true asthmatic, who can expire for only three or four seconds, a patient with this disorder may require up to 12 seconds to achieve his full vital capacity. The timed vital capacity is not improved to any great degree by treatment. Bronchodilators may effect a five-to-ten per cent improvement at best; adrenocortical steroids seem to have no specific effect whatsoever. Skin tests for antigens are negative. These three disorders are not distinct. True asthmatics may develop permanent obstructive changes with emphysema; it is surprising to me how often they do not. As he gets older, a patient with atopic asthma may develop a more persistent and complicated disease with associated chronic infection and more eosinophilia. He may not respond well to control of allergic factors alone. "Asthmatic bronchitis" is a term that is used indiscriminately in many different contexts, but it is probably a real entity in the very young child who develops wheezing during acute respiratory infections and has no subsequent trouble. In the older patient, "asthma" appearing with respiratory infections may reflect underlying obstructive pulmonary disease.

Management

There are significant differences in the management of these separate disorders which are worth emphasizing:

1. Environmental Control

Avoiding respiratory irritants may be beneficial in all these disorders, but it is most important for patients with obstructive emphysema. These people should be advised to stop smoking and to avoid polluted atmospheres. The most effective therapy for atopic asthma is the elimination of offending antigens inside the home. An effective household filtering system may also provide considerable relief for the patient by limiting the influx of pollen, mold spores, and dust.

The decision to advise patients to move to a "better climate" should be influenced strongly by the nature of the basic disease. Atopic asthmatics are often urged to move to a "dry climate" with unfortunate results. Seasonal pollen asthma in New York or Detroit may turn into perennial pollen asthma in the warm, dry, well-irrigated population centers in Arizona or California. On the other hand, patients with non-atopic asthma and obstructive emphysema may improve dramatically in such climates. No patient, however, should be advised to move without a trial period in the new area first.

2. Bronchodilator Drugs

Drugs such as epinephrine or theophylline may be of real benefit in true asthma, but have relatively little effect on obstructive emphysema. It is a common experience to observe patients with this disease use a remarkable amount of nebulized epinephrine or isopropylarterenol in a desperate attempt to get a minor improvement

in ventilatory flow rate. These drugs seem to work only to the degree that mucosal edema is reduced and sputum is increased.

3. Adrenal Cortical Steroids

Both atopic and non-atopic asthma may improve dramatically with steroid therapy; this is reflected by marked improvement in vital capacity and ventilatory flow rate. However, in non-atopic asthma particularly, it is difficult to discontinue steroids. Although steroids may give some subjective relief to patients with chronic obstructive emphysema, they do not improve ventilatory function. Steroid treatment is inadvisable for this latter case since the cost and risk in steroid therapy outweigh the minor subjective benefit.

4. Hyposensitization

When asthma is related to inhaled antigens by information from their history and by specific immediate skin reactions, hyposensitization of the patient with those antigens is clearly beneficial. However, such treatment of non-atopic asthma, has little influence on the course of the disease; indeed, bacterial vaccines may make it worse. The patient with obstructive pulmonary emphysema is sometimes given a long series of such injections on the basis of an incorrect diagnosis of asthma and some minor skin test reactions. A more physiological approach to therapy for that patient would be far more beneficial.

5. Supportive measures

Breathing exercises, postural drainage, sputum liquefiers, intermittent positive pressure breathing, and antibiotic therapy are helpful for the true asthmatic particularly during the early phases of management. Good treatment of chronic obstructive emphysema, however, must depend largely on such measures, since bronchodilator drugs are relatively ineffective by themselves, and steroids are of no value.

QUESTIONS AND ANSWERS

Q. *How can non-atopic asthma be allergic, if the results of skin tests are negative?*

A. The evidence has been circumstantial so far. Eosinophilia is a characteristic finding in the tissues as well as in the blood in these patients. Although skin tests for bacteria are relatively unreliable, a few patients also have been shown to develop asthma when bacterial antigens are injected. The possibility of an autoimmune reaction has also been seriously considered in recent years.

Q. *Does true asthma always start at an early age?*

A. No, I have found that atopic asthma may manifest itself quite late in life. One of my patients developed seasonal asthma for the first time at the age of 68. He was allergic to a specific mold. Non-atopic asthma may also start late in life. I had one patient who was 72 when his symptoms began.

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SURGERY

L. Kraeer Ferguson, M.D.
University of Pennsylvania

L. Kraeer Ferguson is Chairman of the Department of Surgery of the Graduate School of the University of Pennsylvania and Consulting Surgeon at Philadelphia General Hospital and the U.S. Naval Hospital in Philadelphia. In the May issue of CONSULTANT, Dr. Ferguson presented the case for greater use of surgical treatment for gastric cancer. Now, he turns his attention to office surgery, a major interest which culminated in his textbook, SURGERY FOR THE AMBULATORY PATIENT.

OFFICE MANAGEMENT OF ANAL LESIONS

Treatment of anal lesions is not one of the more glamorous chores in medicine, but it is important—important to us because these lesions are so common, and desperately important to the patient because they cause such discomfort. Usually both diagnosis and treatment are office procedures.

Significance of Symptoms

Symptoms are of great significance in diagnosing anal lesions. Ask your patient to describe his symptom or symptoms so that you can fit each into one of the categories listed in Table I. Then using the table as a guide, you can get a fairly accurate idea of the probable cause of the trouble. Pain is particularly meaningful, for it indicates the lesion is distal to the mucocutaneous line. This is because the autonomic nerves of the mucosa above the line do not respond to pain stimuli as do the cerebral spinal nerves of the skin below.

Although symptoms are significant, a rectal and anal examination is needed for accurate diagnosis. A finger cot and lubricant are all the equipment needed in most cases, but a lighted anoscope and a probe bent to form a hook will sometimes be useful. The patient should be examined in the knee-chest position with the side of his face on, and thighs perpendicular to, the table. The knees should be spaced about 12 inches apart for stability.

After examining the perianal area, palpate the anal canal for masses or areas of tenderness. For patient's comfort, painful lesions should be palpated by introducing the finger along the anal wall away from the lesion, then rotating the finger to gently palpate the painful area. The lesions should then be inspected using an anoscope.

Fissure-in-ano

Because of the angle of the anal canal, the passage of a firm stool will stretch and sometimes tear the posterior wall of the anal canal. Usually the tear will heal without symptoms, but sometimes it becomes infected to form an acute anal ulcer. When this happens, defecation is marked by a cutting pain, which persists because the ulcer is caught in the sphincter muscle spasm that results from the irritation of the ulcer. Secondary constipation usually results because the patient tries to delay painful bowel movements.

Conservative treatment of the acute phase of fissure-in-ano consists of avoiding bulky food and administering mineral oil to reduce the trauma of defecation. Hot sitz baths and hot compresses to the anal area after defecation will relax the sphincter muscle and relieve the pain.

However, chronic anal fissures rarely heal without surgery. The procedure is as follows. First infiltrate the ulcer and sphincter with 1% procaine HCl; then partially divide the external sphincter muscle by lightly incising through the base of the ulcer into the muscle beneath. This relaxes the muscle and makes defecation painless. Sometimes partial healing of a chronic fissure heaps up scar tissue to form a hood-like "sentinel pile." The scar tissue should be excised before dividing the sphincter muscle.

TABLE 1

Symptoms	Description	Inference
Pain	Continuous but aggravated by defecation	*Abscess* traumatized by stool
	Caused by, and persisting after, defecation	*Fissure* or *hypertrophic papilla* produced by passage of firm stool
Bleeding	Bright red; small amount on toilet tissue	*Fissure* (tear) in anus produced by passage of firm stool
	Bright red; enough to color water in bowl	Laceration of *internal hemorrhoid* by passage of stool
	Dark blood in stool	Lesion above anal area
	Slight stain on underclothes	Trauma to *prolapsed internal hemorrhoid* or *ulcerated thrombosed external hemorrhoid* caused by clothing
Mass	Appearing only with defecation	Mass due to *prolapsed internal hemorrhoid* or *pedunculated hypertrophic papilla* dragged along by feces
	Present constantly	*Thrombosed hemorrhoid* or *abscess* adjacent to anus
Moisture		Draining *fistula* or weeping *perianal dermatitis*
Itching		*Skin tabs, perianal dermatitis,* or irritation from draining *fistula*

Thrombosed External Hemorrhoid

The thrombosed hemorrhoid usually appears as a hardened, rounded mass, which produces pain, tenderness, and edema. Sometimes the thin skin covering the mass may erode, and dark bloody clots may be discharged.

Inject procaine around and under the mass. Then make an elliptical incision in the skin covering the vein. Lifting one corner of the skin with a hemostat, carry the incision downward to excise the thrombosed vein and overlying skin.

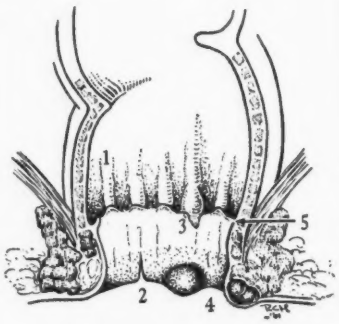
Hypertrophic Anal Papilla

Hypertrophied papillae, which can be palpated as hard nodules in the mid-anal canal, are usually caused by trauma due to the passage of a hard stool. Edema and finally fibrosis permanently enlarge the papillae. If a papilla causes discomfort, it may be excised. Locate the papilla using an anoscope, and inject one or two cc. of procaine with adrenalin into its base. Crush the base of the papilla with a hemostat for a minute or two; then snip off the papilla with scissors.

Postoperative Care

I have found that Gelfoam® makes an excellent soft, hemostatic dressing held in place by a small piece of gauze introduced into the anus. I advise hot sitz baths when the dressing is removed 12 hours after the operation.

Common Anal Lesions



1. Rectal column
2. Fissure-in-ano
3. Thrombosed papilla
4. External hemorrhoids
5. Mucocutaneous line

QUESTIONS AND ANSWERS

Q. *Do you use any protective dressing besides the Gelfoam®?*

A. I find that ordinary Kotex-type pad is the most useful dressing for preventing irritation by clothing. I keep snap-on belts and pads in my office for use by both men and women.

Q. *How do you treat postoperative pain?*

A. Oral codeine usually relieves the slight pain after the anesthetic has worn off (about one hour after surgery). I prescribe a one-half grain codeine sulfate tablet to be taken every three hours if pain is bothersome. Many patients require none at all.

Q. *Can a thrombosed hemorrhoid be treated by simple incision and evacuation of the clot rather than by excision of the vein?*

A. Excision is necessary to prevent further clotting. Also, if the overlying skin is not excised, skin tabs often form, and intense itching results.

GERIATRICS

Eddy D. Palmer, Col. M.C.
Brooke Army Medical Center

Eddy D. Palmer, Col. M.C., is consultant in gastroenterology to the Surgeon General, and is Chief of the Gastroenterology Section at Brooke Army Medical Center, Fort Sam Houston, Texas. He is Clinical Assistant Professor of Medicine at Baylor University Postgraduate School of Medicine and a member of GP's Editorial Advisory Board. In the June issue of CONSULTANT, Col. Palmer described abdominal angina; this month, he turns his attention to another serious medical problem seen in elderly patients.

MEAT IMPACTION IN THE ESOPHAGUS

Sudden obstruction of the esophagus by meat impaction is another of the medical problems that have become more common as the population ages. It is encountered often in old folks' homes but can happen accidentally at any time in the everyday life of elderly people.

Meat impaction has many features common to the impaction of other foreign bodies, yet in many respects the problem it presents is unique. The patient, as I have said, is almost always elderly. Very often he wears dentures. Sometimes his chewing apparatus is faulty and as a consequence he may not always chew his food properly. As might be expected, either a fair degree of general debility or carelessness and haste are obvious at the time of the accident.

As a rule, meat is to blame, almost always either pork or steak, both of which are often tough, stringy, and hard to chew. On rare occasions other meats have been reported as esophagus-stoppers, but I have never seen fish or fowl behave this way unless a bone is swallowed too.

When meat plugs the esophagus, it does so suddenly and completely. Usually it comes to rest in the ampulla, where after the primary peristaltic wave of the esophagus triggers ampullary contraction, peristalsis normally stops. The ampulla, which does not have the ability to promulgate a wave,

empties by contracting its entire length all at once, so this normal contraction only more firmly incarcerates a solid meat bolus, particularly if it is a large one. Generally, stoppage is not caused by an organic obstruction; but, nevertheless, the existence of a previously unrecognized stricture or tumor should be considered upon discovery of the impaction.

When the bolus stops, the patient immediately recognizes that something has happened. He can no longer swallow and every effort to do so results in regurgitation and choking. Tracheobronchial aspiration is a serious threat. Salivation is active. Ordinarily there is some degree of deep retrosternal pain, and this plus the choking may frighten the patient. However, he may not show it. Elderly patients who are depressed may say nothing to anyone about their sensations, and their friends or attendants will merely notice that they have stopped showing up for meals. There are a few who seem to regard the event as unspectacular, and will get themselves into this trouble repeatedly, in spite of the discomfort and inconvenience, and in spite of the explanations and advice of their doctor.

Confirming The Diagnosis

If the patient is at all communicative, diagnosis is ordinarily evident from the history and from the absence of swallowing sounds. If there is suspicion of esophageal obturation, contrast roentgenography should, of course, be carried out, but two precautions are important! First, before any study is made, a tube should be passed and the organ aspirated of its liquid contents, both to discourage tracheal aspiration and to assure a good examination. Second, a soluble agent must be used for the contrast study, for it must be assumed that esophagoscopic examination is imminent.

At fluoroscopy, the obstruction and its location can be recognized, but no more. The configuration of the upper surface of the obstructing mass tells very little about its nature, and the mass itself obscures the presence of any underlying esophageal disease that may be the cause of the bolus arrest.

Esophagoscopic examination is the next step in diagnosis. In some cases esophageal contents aspirated prior to roentgenography may contain recognizable meat fibers, but this tells only part of the diagnostic story, since the existence of an underlying disorder is always possible. Usually the best time for removal of the meat plug is at esophagoscopy. The procedure should not be a particularly hazardous one, but it often proves to be a tedious one for patient and esophagoscopist because the chances are good that the material will have to be picked out bit by bit. The endoscopic field eventually may become obscured by a little bleeding plus the gradual change of the mass to characterless amorphia.

When The Meat Mass Cannot Be Removed By Instruments

If endoscopic facilities are not available, or if kyphosis, aortic aneurysm, or some other deformity or disease makes safe esophagoscopy seem unlikely, the meat mass can be removed by digestion rather than by instruments. To do this, a solution of the powerful proteolytic enzyme, papain, can be used to clear the meat from

the esophagus. Caroid, the refined commercial preparation of papain, is contained in the crude fruit and leaf juice of the American papaw and is well known to cooks as a meat tenderizer.

Before digestion of the bolus can be done, all liquid material from the esophagus above the plug should be aspirated by a Levin tube. Then about 10 ml. of a 5 per cent solution of the enzyme can be instilled. Thereafter, at 15 minute intervals, the patient drinks 5 ml. of the solution until the softened mass slides through into the stomach. The time required varies from less than an hour to several hours. The patient usually recognizes passage of the bolus onwards, but if the status of the lumen seems unclear to the doctor, a tube can be passed again to test esophageal patency.

Digestion treatment is an easy and effective way to handle the problem, but it cannot be recommended for every case because of the possibility that the meat plug contains a spicule of bone. If it does, then the digestive process may bare the bone causing esophageal injury. On the other hand, esophagoscopic removal has the advantages of assured success, plus the opportunity for on-the-spot examination for pre-existing obstructive lesions. As a rule, it is the kindest therapeutic approach.

QUESTIONS AND ANSWERS

Q. *Aside from meat, are there other materials that will cause an impaction in the esophagus?*

A. Hydrophilic gums that have become popular for the treatment of constipation may sometimes plug the esophagus, but aside from these I have seen nothing else that causes this problem with any consistency at all. Of course, large boli of foods other than meat may sometimes catch momentarily, but they almost always pass with only a little delay.

Q. *If the esophageal examination shows no physical abnormalities, can the impaction be pushed into the stomach?*

A. It must be admitted that the manipulation involved in removing the impaction through the esophagoscope may eventually succeed in doing just this. Nevertheless, no attempt should be made to push the plug into the stomach.

AVAILABLE TO READERS: A WALL CHART SHOWING HOW TO STOP PERSISTENT NOSEBLEED

Because of unusual interest shown in Dr. Albert Seltzer's procedure for packing the nose in persistent nosebleed (June issue), CONSULTANT has reproduced his article, in wall chart form, suitable for display in your office or hospital. Free copies may be obtained by writing to CONSULTANT, SK&F Laboratories, 1500 Spring Garden Street, Philadelphia 1, Pa.

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Prescribing information adopted January, 1961.

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SK&F

INTERNAL MEDICINE

Alvan R. Feinstein, M.D.
New York University

Alvan R. Feinstein is Medical Director of Irvington House, a research and treatment center for rheumatic fever and heart disease, and is Assistant Professor of Medicine at New York University School of Medicine. His investigative interest is focused mainly on rheumatic fever and heart disease, and on problems of nutrition; on these subjects, he has published more than 30 articles in various journals. He is a member of the American Federation for Clinical Research, the Harvey Society, and the American Heart Association.

RHEUMATIC FEVER— PROBLEMS IN DIAGNOSIS

Rheumatic fever gets its name from febrile polyarthritis, its most common feature. However, many patients with rheumatic fever may not be febrile, may not have polyarthritis, or may not be rheumatic at all. This variability of symptoms has led to considerable confusion—and erroneous beliefs —about the causes and treatment of rheumatic fever.

Fortunately, recent studies have clarified the disease process involved. They have improved the objectivity and accuracy of auscultation, and have shown that rheumatic fever invariably develops in association with Group A beta hemolytic streptococcal infections. Thus, rheumatic fever may be defined as a post-streptococcal inflammatory state characterized by arthritis, carditis, or chorea appearing singly or in combination.

Clinical Picture

Arthritis, when it occurs, is easy to recognize; however, it should be verified by objective evidence of inflammation in the joints, and differentiated from arthralgia, myalgia, or bone pains. The presence of febrile arthritis should provoke a search for associated carditis. Keep in mind, however, that carditis is too often "found" where it does not exist. If carditis is absent in a patient with febrile arthritis, rheumatic fever remains a likely diagnosis unless sequential tests of several antibodies fail to show a streptococcal infection, or unless the arthritis does

not respond to appropriate therapy; in that case, you need to rule out lupus erythematosus, rheumatoid arthritis, gout, sickle cell disease, or other alternative diagnoses.

Chorea

Chorea, present in about 8% of rheumatic fever attacks, generally takes longer to develop after a streptococcal infection than arthritis or carditis. Hence the chorea often begins late in a rheumatic attack, as the arthritis and/or carditis are subsiding, or afterwards. Or it may occur as an isolated manifestation, without rheumatic features. In this situation, the preceding streptococcal infection often cannot be demonstrated because the antibodies have returned to normal levels by the time the chorea begins. Chorea, although uncommon, is not usually a diagnostic problem; it can be differentiated from cerebral palsy by its history of recent onset, and from habit spasms or nervous hyperkinesia by its nonrepetitive, purposeless, subjectively uncontrollable movements.

Carditis

Carditis is the most serious manifestation of rheumatic fever and the one most subject to diagnostic error. The greatest difficulty stems from the fact that post-streptococcal carditis can occur without concomitant arthritis and chorea, and it may not produce any discomfort. In such an instance, the carditis will go unrecognized simply because the patient does not seek medical attention.

In patients whose rheumatic fever does produce symptoms, the presence of carditis is recognized by one or more of four features: (1) significant cardiomegaly, (2) pericarditis, (3) congestive heart failure, and (4) significant murmurs. Before considering these four features, I would like to mention that prolongation of the P-R interval in the electrocardiogram is no longer considered evidence of carditis. Although P-R prolongation occurs in 20% to 40% of patients with rheumatic fever, it is an electrical rather than a histopathologic phenomenon and it appears to be due to biochemical factors present in post-streptococcal inflammation. P-R prolongation may be present in patients with carditis, but it alone is not indicative of carditis.

Cardiac Enlargement

Children and adolescents have mobile hearts whose size and shape can change with respiration and phases of the cardiac cycle. Before deciding that the heart has changed size in two different films, you must make proper allowance for position of the diaphragm and the possibility that one film was taken in systole and the other in diastole. In my experience, the criteria for "normal" and "slight" heart enlargement can vary so greatly among different observers that I reserve the term *significant cardiomegaly* only for patients who have at least moderate enlargement (i.e., 2^+ on a scale of 0 to 4^+) of one or more cardiac chambers. Two other frequent errors in x-ray interpretation occur when a normal, prominent pulmonary artery segment is overread as a "mitralized heart," and when minor indentations (usually due to air) of one wall of the barium esophogram are erroneously attributed to atrial enlargement.

Pericarditis

A pericardial friction rub is usually unmistakable evidence of pericarditis. Most errors in the diagnosis of peri-

carditis occur because of unfamiliarity with the wide range of normal variations in the electrocardiogram in children and adolescents. Two common errors are to attribute abnormality to: S-T segment elevations or T-wave inversions in leads V_1-V_4 (which can be normal in younger patients); and nonspecific T-wave changes that can result normally from respiration or changes in placements of the precordial leads.

Congestive Heart Failure

In young rheumatics, congestive heart failure may be asymptomatic or may produce left-sided symptoms (such as dyspnea, cough, and chest discomfort) without corresponding left-sided signs. Its main signs may be tender hepatomegaly, venous distention or ankle edema. Patients are sometimes mistakenly considered to be dyspneic and in failure when their respirations actually are shallow because of the anxiety of hospitalization, or because of pleuritic pain of pericarditis, or rapid because of salicylate toxicity. Congestive heart failure in rheumatic heart disease occurs only in the presence of significant organic murmurs.

Significant Organic Murmurs

The hallmark of rheumatic heart disease and the sign for which the stethoscope remains a crucial diagnostic tool is the organic murmur. In the acute stages of the disease, murmurs can be present in four forms:

(1) the blowing decrescendo diastolic murmur of aortic regurgitation

(2) the crescendo pre-systolic rumble of mitral stenosis

(3) the rough, short mid-diastolic murmur of mitral valvulitis

(4) the blowing systolic murmur of mitral regurgitation.

Errors Of Omission

Two errors are common. The aortic regurgitant murmur is often not detected when present either because it is mis-timed as systolic, because the examiner fails to listen for it in its customary location along the lower left sternal border, or because the examiner is not accustomed to its sometimes-soft and high-pitched quality.

The pre-systolic rumble of mitral stenosis is often missed when it is present, not because the examiner has failed to find it, but because such patients frequently do not have rheumatic, choreic or congestive symptoms and hence do not reach medical attention during the acute attack. In both instances, the murmurs are discovered later and are then thought to have developed insidiously, when actually they have been continually present but undetected.

Errors Of Commission

Again there are two common ones. A long physiologic third heart sound is mistakenly considered to represent a mid-diastolic murmur. Here, the differentiation can be made by noting that the true mid-diastolic murmur occurs invariably in association with an organic apical systolic murmur (as described below). When a third sound occurs in diastole in a patient without a systolic murmur at the apex, it can be confirmed as mitral stenosis only if, after exercise, it becomes presystolic and rumbles into the first heart sound. Otherwise, it is most likely physiologic.

The most common auscultatory error in rheumatic fever occurs in differentiating apical systolic murmurs into those that are physiologic and those that are organic. Since 50% to 90% of normal children have physiologic systolic murmurs arising in the pulmonary valve-artery area, *it is common rather than exceptional to find systolic murmurs in any ill child.* Such physiologic murmurs, which are usually loudest in the pulmonary artery area or along the left sternal border, may frequently be heard at the apex, may occasionally be transmitted to the axilla, and may even, due to the acoustic properties of blood flow, be high-pitched and blowing. Hence, a loud, high-pitched, blowing apical systolic murmur that transmits to the axilla may erroneously be considered organic when it is actually physiologic. Because physiologic and organic murmurs both arise from blood flow, exercise and certain changes in position will make them both louder and cannot be used to separate them. The three main properties that *can* be used to separate a physiologic from an organic apical systolic murmur are:

(1) *duration:* the organic murmur is holosystolic and usually merges with the first sound, often extending into the second sound. The physiologic murmur is short, and may often begin after the first sound, ending before the second sound.

(2) *site of maximal intensity:* the organic murmur is loudest at the apex and to the left of the apex. The physiologic murmur is loudest medial to the apex or along the left sternal border. A systolic murmur audible anywhere in the thorax which is just as loud or louder than the one at the apex must be suspected of being the source of the murmur at the apex, even if it appears to have a somewhat different pitch and quality. The common notation found on many charts of "systolic murmur at apex radiating to left sternal border" is usually incorrect and should be "systolic murmur at left sternal border, radiating to apex."

(3) *effect of respiration:* with inspiration, which affects the position of the pulmonary artery, the intensity of the physiologic systolic murmur at the apex is sharply reduced, or the murmur may vanish. The intensity of the organic apical murmur is substantially unaffected by this maneuver.

Relationship Of Murmurs To Prognosis

Accurate auscultation is not only important for diagnosis but also for prognosis, since patients who do not have any of these significant murmurs during the acute rheumatic attack will not develop rheumatic heart disease. Previous studies that showed the "insidious development" of rheumatic heart disease in patients who were initially free of it are now believed to have contained significant errors in auscultatory and follow-up procedures. Of the patients who have only systolic murmurs during the acute attack, only about 25% will have residual heart disease. Of those who have diastolic murmurs, with or without systolic murmurs, about 50% will have residual heart disease. Of those who have significant cardiomegaly and/or congestive heart failure, about 80% will have residual heart disease. Pericarditis *per se*, if not associated with any of the above factors, subsides without residua.

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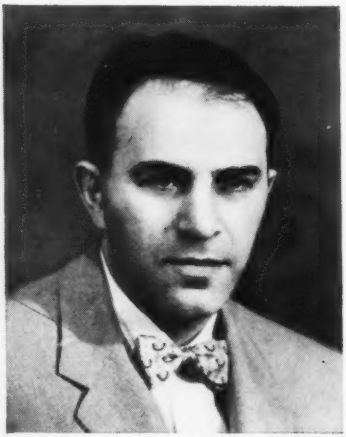
CARDIOLOGY



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CARDIOVASCULAR CLUES DERIVED FROM PULSATIONS IN THE NECK

Careful inspection of the neck veins and arteries takes only a few minutes, can be performed at the bedside, and provides a surprising number of diagnostic cardiovascular clues. It should be an integral part of every cardiac examination.

Congestive Heart Failure

In a recumbent patient whose head is raised to approximately 45°, and rotated slightly, the cervical veins normally are empty and pulseless. In congestive heart failure the jugular veins are distended and, depending on the degree of venous hypertension, a distinctive venous pulsation is observed. The key to venous pressure measurement at the bedside is the height of the "jugular meniscus," that is, the highest level at which the rise and diastolic collapse of the jugular pulse is observed. The higher the level of the "jugular meniscus," the greater the congestion and the higher the pressure. A tensely distended vein will not pulsate. External jugular veins that are both tortuous and engorged signify chronic venous hypertension of long standing.

Venous pulsations in the neck must not be mistaken for arterial ones. Proper lighting as well as positioning of the patient is important to distinguish them. The light, preferably from a flashlight in a darkened room, should shine tangentially across, rather than directly at, the neck. (See

illustration.) Venous pulsations are more diffuse, less easily palpable, and more sensitive to changes in posture, respiration, or abdominal pressure.

One of the earliest clinical clues to congestive heart failure is an abnormal hepatojugular reflux, characterized by intensification and maintenance of neck vein distention when pressure is applied over the liver or abdomen of a recumbent patient.

Incipient Heart Failure

Observation of the neck veins after a simple exercise test can be of real value in the diagnosis of incipient heart failure. In patients with limited cardiac reserve, whose neck veins are ordinarily inconspicuous, slight exertion is apt to produce striking engorgement of the neck veins that persists for several minutes after the exercise has been stopped.

Arrhythmias

The diagnosis of atrial fibrillation based on flutter waves in the jugular pulse is difficult and unreliable. But gross irregularity of the carotid pulsations may be sufficiently apparent to establish the diagnosis.

The diagnosis of a "mid" or "low" AV nodal rhythm may be suspected by the regular appearance of extraordinarily large positive pulse waves in the neck veins. These large waves in the neck are known as "Cannon A" waves, and are produced by contraction of the right auricle on a closed or closing tricuspid valve. "Cannon A" waves may also be observed with ventricular premature beats.

"Cannon A" waves are also helpful in differentiating between ventricular and supraventricular tachycardia. In ventricular tachycardia, irregular, independent "Cannon A" waves occur. They do not occur in supraventricular tachycardia, except in the unusual instance of AV dissociation with AV nodal tachycardia and retrograde block.

Superior Vena Cava Syndrome

One of the most striking features of the superior vena cava syndrome is the intense engorgement of the veins of the neck and upper part of the body. The engorged cervical veins resulting from mediastinal obstruction are pulseless.

Aneurysm of the Aorta

Any unusual arterial pulsation in the lower neck should suggest the possibility of an aneurysm of the arch of the aorta. Heaving pulsations in the suprasternal notch and a systolic lifting of the manubrium may be observed. Marked inequality in the strength of the carotid pulsations is another clue that should suggest an aortic aneurysm. An enlarging aneurysm that obstructs the superior vena cava will cause bilateral, nonpulsating engorgement of the neck veins. Rupture of an aneurysm into the right side

of the circulation will convert venous pulsations of the neck to arterial.

Dissecting Aneurysm of the Aorta

Vigorous pulsation in either the right or left sternoclavicular joint suggests a diagnosis of dissecting aneurysm of the aorta rather than myocardial infarction. So does an inequality of the carotid pulsations. Rarely, the superior vena cava syndrome with marked distention of the neck veins is a manifestation of aortic dissection.

Aortic Insufficiency

In free aortic insufficiency, or regurgitation, the arterial pulsation is characterized by a quick, sharp rise, and an abrupt collapse. This jerky pulsation in the suprasternal notch and along the lateral side of the neck may be pronounced enough to suggest the diagnosis at a glance.

The rhythmic backward movement of the head and neck with each systole, occasionally observed in aortic insufficiency, is known as the sign of De Musset.

Aortic Stenosis

A small, lazy pulsation at the carotids, in contrast to a powerful impulse at the apex, is a feature of advanced aortic stenosis. A palpable, double-peaked carotid pulse followed by an abrupt collapse (which is sometimes mistaken for coupling), is a reliable sign that significant regurgitation is also present.

The Kinked Innominate Vein Or Kinked Carotid Artery

In contrast to the bilateral venous hypertension of heart failure, unilateral engorgement of the left jugular vein suggests a high and probably rigid aorta that is compressing the left innominate vein from below. Interestingly, a pulsating mass at the base of the neck, right or left, and sometimes in the suprasternal notch, may be caused by a high aortic arch secondary to hypertension and arteriosclerosis. While the kinked innominate vein occurs equally as often in men as in women, the kinked carotid occurs almost exclusively in women.

Tricuspid Insufficiency Or Stenosis

Extraordinary pulsations in the neck veins occur in the patient with advanced tricuspid insufficiency. His veins are characteristically engorged and during systole, a powerful, positive jugular pulsation is observed. This powerful venous systolic thrust actually may lift the sternocleidomastoid muscle and is often mistaken for a carotid pulsation. A precipitous collapse of the jugular pulse coincident with diastolic expansion of the chest is a feature of advanced tricuspid insufficiency.

In contrast to the powerful systolic pulsation that occurs in tricuspid insufficiency, tricuspid stenosis is characterized by a positive presystolic wave in the jugular pulse. This presystolic pulsation does not change with change of posture and is present only when cardiac rhythm is regular. A diastolic collapsing type of jugular pulse is never observed. Placing the patient with tricuspid stenosis in a recumbent position will cause intense congestion and cyanosis of the face, and distention of the veins of the neck and head.

A thorough and careful physical examination of the cardiac patient may yield enough diagnostic clues to limit the need for more sophisticated, time-consuming and expensive tests.

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OBSTETRICS

Denis Cavanagh, M.D.
University of Miami

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THE SUSPICIOUS PHYSICIAN: GREATEST SAFEGUARD IN ECTOPIC PREGNANCY

About 20,000 women in the U.S. will have ectopic pregnancies this year. Their chances for survival depend more upon the alertness of the first physician who sees them than upon the surgeon who operates – even though the treatment is always surgical–for prompt surgical intervention depends upon early diagnosis. But how can this difficult diagnosis be made more surely and quickly?

The techniques suggested here are used at our hospital but are entirely suitable for office practice. They have effectively increased the speed and certainty of diagnosis at Jackson Memorial Hospital, where we see one ectopic pregnancy for every 53 babies born on the ward service (compared to the national incidence of about one in 200). Our considerable experience has taught us to depend upon one of the newer diagnostic techniques, culdocentesis, as well as the traditional signs and symptoms.

When To Be Suspicious

A suspicious physician is the patient's greatest safeguard against the dangers of ectopic pregnancy. Of course, ectopic pregnancy must always be suspected when a woman of childbearing age complains of lower abdominal pain. But suspicion should increase if she has had a previous ectopic pregnancy because one ectopic pregnancy is frequently followed by a second. Also, we are especially suspicious when dealing with women in the lower socioeconomic group because gonorrhea is a frequent precursor of ectopic pregnancy. Over half of our patients with ectopic pregnancy have a history of gonococcal salpingitis; moreover ectopic pregnancy seems to be even more common among patients who have received inadequate antibiotic treatment.

The Symptoms

Rarely does the patient seek medical advice before the ectopic pregnancy ruptures. Her symptoms seem insignificant—often just a vague, colicky pain in the lower abdomen and amenorrhea lasting 5 to 8 weeks. Because there is seldom an opportunity to diagnose ectopic pregnancy before it ruptures, early diagnosis after rupture is vitally important.

Sudden exacerbation of abdominal pain usually signals the rupture. Marked tenderness over the lower abdomen and "rebound" pain are almost always noted. Referred pain in the shoulder is fairly common but an unreliable guide as to which tube is involved. Abdominal distension and muscle guarding are present in varying degrees. Pelvic examination usually reveals a tender adnexal mass with excruciating unilateral pain when the cervix is moved. Vaginal spotting almost always occurs. Other common symptoms are the urge to defecate, urinary frequency, fainting and nausea.

Culdocentesis: When And How To Do It

In a woman with the foregoing symptoms—indeed in all young women with irregular vaginal bleeding and unexplained lower abdominal pain—culdocentesis should be performed. The increased use of this simple office procedure will surely reduce deaths from ruptured ectopic pregnancy by enabling physicians to detect blood in the peritoneal cavity at an earlier stage. Routine use of this test at Jackson Memorial Hospital has reduced the time from admission to operation for ectopic pregnancy from 2 days to about 2 hours.

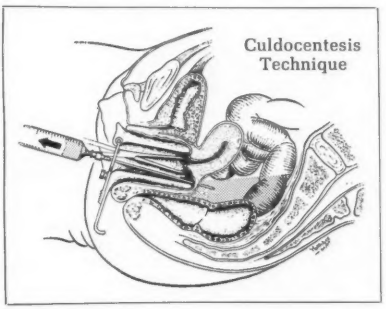
No local anesthesia is used. If the patient is uncooperative, give her 25 to 50 mg. of intravenous Demerol® slowly. Just before beginning the procedure, place the patient in the sitting position for a few minutes, so that any blood in the peritoneal cavity will gravitate to the cul-de-sac. Ensure by a bimanual examination that a retroverted uterus is not occupying the cul-de-sac where it might be damaged by culdocentesis. Then proceed as follows:

(1) Place the patient in the lithotomy position, and gently cleanse the vagina with antiseptic solution.

(2) Grasp the posterior lip of the cervix with a tenaculum, and raise the cervix to expose the posterior fornix.

(3) Wipe the mucosa clean with sterile gauze.

(4) With a quick movement, insert an 18-gauge spinal needle about 1 cm. below the junction of the cervix with the vaginal mucosa. The needle should penetrate about 2 cm.



(5) Apply intermittent suction as the needle is withdrawn.

Finding free, unclotted blood in the peritoneal cavity helps differentiate ectopic pregnancy from acute salpingitis, acute appendicitis, and acute pyelonephritis. With a normal temperature, a hematocrit low or falling, a

WBC of 12,000 per cu. mm. or less, a positive culdocentesis generally confirms the diagnosis of ruptured ectopic pregnancy. True, a ruptured hemorrhagic corpus luteum cyst gives the same picture, but a laparotomy is needed to control bleeding in either case, so differentiation between these two conditions is of academic rather than practical importance.

QUESTIONS AND ANSWERS

Q. *What are the complications of culdocentesis?*

A. We have seen no significant complications in over 2,500 cul-de-sac taps, performed mainly by interns and residents at the Jackson Memorial Hospital. Most of these taps were carried out in the emergency room, using standard office equipment. Although in a few cases, blood was aspirated from pelvic blood vessels, or flatus from the bowel, neither these women nor two others who had inadvertent "fecal biopsies" showed ill effects from off-target probes.

Q. *What if culdocentesis produces 2 or 3 cc. of blood which clots within 2 or 3 minutes?*

A. This probably means that you've hit a pelvic blood vessel. Repeat culdocentesis immediately. In the presence of a hemoperitoneum you may see a few fragments of clot, but the blood as a whole does not clot.

Q. *If no fluid whatever is aspirated from the cul-de-sac, should this be classified as a negative tap?*

A. This should be regarded as another off-target probe. You should aspirate a few drops of peritoneal fluid on culdocentesis. Failure to withdraw fluid from the cul-de-sac, like failure to withdraw blood from an arm vein, should suggest that your needle is not where it ought to be. The tap should be repeated.

Q. *Is the aspiration of non-clotting blood from the cul-de-sac diagnostic of ruptured ectopic pregnancy?*

A. No. It merely means that hemoperitoneum is present. Recently I saw a woman with a positive culdocentesis and a history consistent with a ruptured tubal pregnancy, but laparotomy revealed a lacerated liver. (Later I discovered that she had been kicked in the abdomen by her husband but, like a loyal wife, had failed to mention this rather pertinent piece of history.) Since exploratory laparotomy should be done for hemoperitoneum, whatever the etiology, such a case as this can scarcely be regarded as a therapeutic failure. In a young woman with lower abdominal pain and menstrual irregularity, by far the most common cause of hemoperitoneum is a ruptured ectopic pregnancy.

Q. *What is the value of obtaining a pregnancy test when an ectopic pregnancy is suspected?*

A. Very little. In about one-third of the cases it is negative, and valuable time is wasted in awaiting the result. A pregnancy test is of value only in the atypical or chronic type of ectopic pregnancy.

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Though the photographs above were professionally posed, they faithfully reflect case histories that are brought to our attention almost daily—histories that explain the widespread acceptance of 'Thorazine' (brand of chlorpromazine) as a fundamental drug in both office and hospital practice.

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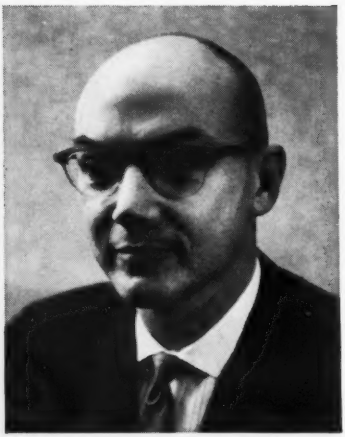
PSYCHIATRY



Blaine E. McLaughlin, M.D.
Woman's Medical College of Pennsylvania

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HELPING THE AGGRESSIVE ADOLESCENT

The boy had been arrested for reckless driving in a stolen car. The police had released him, at least temporarily, and his parents, who were friends of mine, wondered "if you could talk to him, maybe straighten him out. He's always respected you and . . ." I did talk to him, and I was able to "straighten him out." Six short interviews with the boy, a letter to the local chief of police, and some explanation and advice to the parents were enough to reduce a potentially dangerous situation to a routine problem of "growing up". And the family physician could have handled this problem just as easily. In fact, the family physician can probably handle about 90% of the adolescents who get into trouble with the community and need help.

But which ones are beyond your help? What about the boy who tells you he wants to shoot his father? Or the girl who is promiscuous and may have already had one illegitimate child? Should you try to handle them, or should you refer them? It depends. I would like to outline an approach that will let you help the youngsters you can help, and identify the ones you cannot.

The "Normal" Adolescent

Rebellious testing of authority is the usual or "normal" form of emotional expression during adolescence. The youngster cannot escape for a Florida vacation or a reconditioning in the beauty shop—and the channeling of young energy into family chores is, by and large, vanishing. So he strikes out in some symbolic way against the general authorities. Up to a point, society will accept this behavior; beyond it, the behavior becomes

definitely unacceptable—but not necessarily pathologic.

Consider the boy I mentioned at the beginning of this article. He was a member of one of the best families in a middle class neighborhood and had had a fairly good academic record. But he had begun to lose interest in his school work and to be truant on occasion. His father was a self-made man, proud of it, determined to maintain or improve his position, and devoted most of his time and energy to seeing that he did. His mother was over-indulgent, unrealistic, and confused. Neither parent had been able or willing to cope with the boy's developing male personality. While this was a potentially explosive mixture of fatherly pride, motherly confusion and boyish aggressiveness, there was no real psychiatric pathology present—yet. The boy's episodes of misbehavior were mixed with periods of exemplary conduct, and he generally demonstrated the unpredictability that is, or should be, expected during adolescence. Actually, it is the youth who presents a constant, unchanging front—"good" or "bad"—who should cause us more concern. This case is typical of the thousands of "acting out" adolescents who will not respond to help offered by other authorities, but who can be handled by family physicians in the day-by-day routine of out-patient practice, when other authorities have failed. Why? Well, a large part of your potential success is "built-in"—is there simply because you are a *doctor*. Because the doctor, though identified with authority, still represents help against the other forces of the community.

Here is a youngster in trouble. He has lost his rapport with the school teacher, may never have had any with the police, and has certainly strained the understanding of his parents beyond the breaking point. Now he has a chance to identify with the doctor—a recognized authority in the community. He has a chance to tell his story to an authority who will not only be neutral but will, if possible, take his side. Fifteen minutes *alone* with him can be worth more than two hours with the district judge, or days of lecture by outraged parents.

The Interview

I cannot tell you, of course, exactly what you should say. But as long as you remember that your purpose is to establish or reinforce the youngster's belief that you are interested in him and in helping him help himself; that you understand his action, although you can't approve it, you will not go far wrong. This means, of course, that you must *be* genuinely interested and prepared to offer understanding and support. You cannot fake it. The youngster is already wary and will notice the insincere inflection, or the forced facial expression, other nonverbal clues that signal pretended interest—he has probably seen them before. In short, if the youngster's behavior is personally unacceptable or offensive, don't try to handle him. You will seldom be successful and, by giving him cause to suspect "doctors" as well as all other authorities, will probably make it that much harder for any other physician to help him.

That you must be genuinely interested does *not* mean that you should be passive. It would be very easy to sit back and let the youngster ventilate—express his hostility toward his parents and the community openly. To let

him complain that "one day I can't do something because I'm not old enough, and the next I can't do something because I'm too old. Why don't they make up their minds." It would be easy, but unless you are prepared to spend ten or fifteen hours listening to this sort of thing, it will not help much. Fifteen minutes of pure ventilation is simply useless. You don't have to say "now tell me about your problem," which almost has to lead to ventilation, to show that you are interested in him. It is often easier, and much quicker, to establish rapport and break down his resistance toward authority and skepticism by talking about something that interests him. In our example, I started by telling the boy about my interest in hot-rods and my sincere belief that the city should have a drag-strip where young people could test their cars in competition. Within ten minutes, he was discussing problems of cam-shaft construction that were well beyond me. He obviously knew more about automotive engineering than almost any adult layman. I honestly admired his knowledge and I showed it. Then I told him what I knew of his problem, listened to his version of the situation and said, "Look, this is a complex problem. I want some time to think about it and I want you to think about it, too. I want you to take these pills to cut down your tension for the next few days while you try to work out what you can do about it and what I can do to help. In the meantime, I'm going to talk to your parents about it. Come back on Wednesday and tell me how I can help."

Interview With Parents

There are two things you hope to accomplish during an interview with the parents. First, you want to get them to agree on what they want or expect from the youngster. This may be the first time they have really tried to think it through. Second, you want to get them to recognize your patient's point of view, and whatever shortcomings may exist in their understanding of the youngster's needs. The alternative to accepting your criticism —the possibility of jail for their child —will usually make them receptive.

Second Interview With Youngster

During this interview, ask him what steps he would suggest to improve the situation (be ready to make suggestions if he doesn't have any). In our example, the boy made six suggestions. They were, and almost always are, obvious and expected. Boiled down, he wanted greater freedom, no probation, and a car (a 1932 Ford Roadster he could convert) of his own. I told him I would do what I could to get his parents to buy him a car, but that he would have to reconcile himself to the probation, get a job to pay for the conversion of the car, and submit to his parents' rules for behavior. He accepted, so did his parents. A potentially dangerous problem was resolved.

Psychiatric Referral

This relatively simple and practical approach will not always work, but after one or two short interviews, you should be able to tell which adolescents can be helped and which ones need to be referred. The behavior of the adolescent who uses your understanding as a weapon against others, either the family or the community, is definitely pathologic. When he distorts your counsel and offer to help into approval of his actions, or justi-

fications for even more unacceptable behavior, he should be referred. If, for example, the boy who has stolen a car turns around after counselling and steals another one only to say when caught, "Doctor Smith understands me. He says it is normal and all right," he should be referred.

There are other obvious problems that may develop and make referral necessary; for example, you may establish a good relationship with the boy, decide on a practical solution, and then find that the parents refuse to go along. Refer. If you cannot make good on your end of the bargain, you will not be able to help much. If the youngster's suggestions are all impossible—for financial or any other reason—and he will not accept any practical modification—again, refer.

In short, if the youngster or his parents will not accept your advice or mediation, or seem to accept it but distort it, refer the patient to someone who can attempt more extensive and time-consuming methods (like free ventilation). Most youngsters, though, will respond to this type of identification and supportive therapy.

QUESTIONS AND ANSWERS

Q. *This approach seems to require that the adolescent be at least fairly intelligent. What about the mentally retarded or deficient youngster?*

A. This kind of therapy does require intelligent cooperation, and probably won't work with an adolescent whose intelligence is significantly below normal. He should be referred. In making a decision concerning his intelligence, however, do not be misled by school grades. If the youth with very poor grades and no apparent interest in academic work does have an interest and knowledge of some other field, he is probably intelligent enough to benefit. I think it foolish, for example, to consider retarded the boy who can discuss the relative merits of AC and DC motors, or when you should use "tri-X" instead of "hypan" film. Misdirected or single-minded perhaps, but retarded or deficient, no.

Q. *Can this approach be used for youngsters who aren't in trouble yet but who seem headed for it?*

A. I doubt it. Actually, one of the factors on your side with the boy who is in trouble with the police or other authorities outside the family is the fact that he *knows* that he is in trouble, that he can't ignore it, and that the excuses he's used with his parents won't work in this situation. He, like his parents, also knows that your recommendation will have a lot to do with the final disposition of his case. In effect then, it is usually harder to help the adolescent who *may* get into trouble, than it is to help one who *is* in trouble. It will certainly take more time.

your advice, his cooperation, plus a prescription for ACNOMEL®...

Your advice on proper skin care, hygiene and diet, the patient's cooperation and a prescription for 'Acnomel' are often all that are necessary to control acne.

'Acnomel' Cream is a basic topical preparation for acne treatment. Sulfur and resorcinol reduce oiliness, dry the skin and produce a keratolytic effect. Hexachlorophene reduces the possibility of bacterial infection.

Grease-free, easy to apply and to remove, flesh-tinted 'Acnomel' Cream conceals acne lesions as it heals them. Thus patient embarrassment about unsightly acne pimples and blemishes is greatly relieved.

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Prescribing Information:

TWO CONVENIENT FORMS: 'Acnomel' Cream (sulfur, 8%; resorcinol, 2%; hexachlorophene, 0.25%; in a stable, grease-free, flesh-tinted vehicle). Standard strength for home application, morning or night. 'Acnomel' Cake (sulfur, 4%; resorcinol, 1%; hexachlorophene, 0.25%; in a washable, flesh-tinted cake base). Half-strength, in handy plastic containers, for convenient use away from home.

ADMINISTRATION: Cream: One application daily is usually sufficient. Patients with oily skin may apply more often. Apply in small amounts with finger tips. Keep out of eyes and off eyelids.

Cake: Apply 2 or 3 times daily, as required, to treat and mask individual lesions. Dab on gently with finger tips or damp sponge.

To shorten the course of acne therapy, 'Acnomel' Cream may be prescribed for application at night and 'Acnomel' Cake for daytime use.

CAUTIONS AND CONTRAINDICATIONS: Moderate erythema and scaling are normal and are expected results of 'Acnomel' therapy. However, should these reactions become excessive, the patient should apply 'Acnomel' less frequently or discontinue until they subside. 'Acnomel' should not be applied to diffuse, acutely inflamed areas. Keep out of eyes and off eyelids.

AVAILABLE: Cream—in specially lined 1½ oz. tubes; Cake—in convenient 1 oz. plastic containers.

Prescribing information adopted January 1961.

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'Eskatrol' *Spansule* capsules provide daylong control of appetite *and* relief of the psychic stress that causes overeating. Because the tranquilizer component of 'Eskatrol' controls emotional stress, your patient has a better chance of staying on his diet —even for prolonged periods of time.

ESKATROL® SPANSULE®

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Prescribing Information

FORMULA: Each 'Eskatrol' *Spansule* sustained release capsule contains Dexedrine® (brand of dextro amphetamine sulfate), 15 mg., and Compazine® (brand of prochlorperazine), 7.5 mg., as the dimaleate, distributed among hundreds of minute pellets with varying disintegration times. A therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours.

IN OVERWEIGHT PATIENTS: 'Eskatrol' *Spansule* capsules are indicated in overweight patients, particularly in those who depend on eating for psychologic release.

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RECOMMENDED DOSAGE: One 'Eskatrol' *Spansule* capsule daily, taken in the morning.

SIDE EFFECTS: Side effects (chiefly nervousness and insomnia) are infrequent, and usually mild and transitory.

CAUTIONS: Clinical experience has demonstrated that 'Eskatrol' (containing the phenothiazine derivative, 'Compazine') has a wide margin of safety and that there is little likelihood of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence.

'Eskatrol' *Spansule* capsules should be used with caution in the presence of severe hypertension, advanced cardiovascular disease, or extreme excitability.

Adopted Jan. 1961

AVAILABLE: In bottles of 30 and 250 capsules.

Smith Kline & French Laboratories

SK&F

PEDIATRICS

Keith Hammond, M.D.
Muncie Clinic, Muncie, Indiana

Keith Hammond is a member of the Pediatric Department of the Muncie Clinic, and Associate in Pediatrics at the Ball Memorial Hospital in Muncie, Indiana. A recipient of the Wyeth Fellowship in Pediatrics, he is the author of fifteen published reports on various aspects of child care. He has served on the editorial staffs of GP and PEDIATRIC CLINICS OF NORTH AMERICA. His professional affiliations include the Muncie Academy of Medicine, the Indiana and Kentucky Pediatric Societies, and the American Academy of General Practice.

WHEN TO USE ANTIBIOTICS FOR RESPIRATORY INFECTIONS IN CHILDREN

The problem of whether or not to administer antibiotics in respiratory infection is a common one, and is complicated in two ways: first, we must guard against overuse of antibiotics, particularly in children; second, laboratory tests to identify the organism causing the infection are not always practical. Even so, I believe that *rational* use of antibiotics is possible anywhere—if clinical good sense is applied.

Treating Croup

Suppose, for instance, that you are treating a young child for croup. You have concluded that there is no reason to suspect diphtheria, and the blood count and appearance of toxicity suggest that the infection is bacterial. Because *Hemophilus influenzae* is prone to invade the larynx, and because it causes a particularly severe form of croup, there is a rational basis for beginning treatment immediately with an antibiotic effective against *H. influenzae*—chloramphenicol, streptomycin, or perhaps a sulfa. In this instance, a delay in treatment until a culture could be grown could be hazardous and would not be justified. The other pertinent laboratory procedure—a sensitivity test—could only confirm that the organism was sensitive to the drugs already chosen.

Viral or Bacterial?

In children, as in adults, the most important decision is whether or not the infection is viral or bacterial. Simply

knowing this usually leaves little else that need be learned in order to treat the patient rationally. Therefore, the decision whether or not to use an antibiotic, and if so, which one, can be made with reasonable accuracy, simply on the basis of clinical judgment and knowledge of a few points about respiratory infections.

Some Helpful Points

Here are five such points I consider most helpful to remember: (1) viral infections do not respond to antibiotics, (2) most respiratory infections (some say as many as 90%) are viral rather than bacterial, (3) antibiotics should seldom be used as a prophylactic measure in respiratory infections, (4) there are only a relatively few bacteria that cause clinically recognized conditions in any given part of the body, and (5) *in vitro* sensitivity tests are of no value unless one first isolates and identifies the responsible organism (once the organism has been identified, sensitivity tests are likely to be confirmatory and helpful only when the infection is resistant to an antibiotic).

Clues to Etiology

Points 1 through 3 are too well known to need elaboration, so let us go to the fourth point. Over the years it has become evident that certain clinically recognizable conditions are caused by certain identifiable organisms. This has already been mentioned, for example, in the case of acute laryngitis in children. If croup is bacterial, it is almost always due to *H. influenzae*, especially since diphtheria has become such a rarity. Also, when obstruction is due to the dreaded acute epiglottitis the influenza bacillus should be the prime suspect.

Pneumonia presents a similar situation. When clinical signs point to a bacterial infection, we may deduce that it is probably due to one of three organisms: pneumococcus, streptococcus, or staphylococcus. All three types will respond, to some extent, at least, to penicillin. Only if the infection is due to a resistant strain of staphylococcus will a different drug be needed; usually, though, a staph infection is contracted from a hospital source so the history is important.

Pharyngitis is another example, one where we are prone to throw reason to the winds. Penicillin has become for the sore throat what rock and rye were for the common cold. This is true even though pharyngitis is far more commonly viral than it is bacterial. In fact, when streptococcal infection is not prevalent in the community, it is almost as rare as measles is when the measles virus is out of season. Not all that is exudative is streptococcal, and researchers have gone to great pains to demonstrate that the staphylococcus does not cause sore throat.

Sensitivity Tests

Finally, let us consider my fifth point: that sensitivity tests have limited practical value, and then only when the infecting organism has been identified. Many innocent bacteria can be grown from a diseased mucosa, so unless there is a good reason for suspecting the sensitive organism, the test is useless. It is not my purpose to belittle the value of the laboratory, but I do contend that clinical judgment and knowledge still form a rational basis upon which one can frequently make a decision.

Admittedly, there are situations in which the rational choice of an antibiotic is difficult, even when evidence points to a bacterial infection. I am thinking of infections such as otitis media, when even a culture may not grow the responsible organism. On the other hand, there are times when one may want to start treatment pending completion of laboratory studies. Under such circumstances, as with suspected meningitis, it would not be improper to administer multiple antibiotics.

In conclusion, I would like to simply reiterate that before one yields to the premature urge to give antibiotics to a child with a respiratory infection, it is wise to stop and consider that the cause is viral in the vast majority of such cases. Furthermore, much of what seems to be viral is actually allergic. Then, as a final discouragement to the overuse of these drugs, it should be remembered that they are not indicated prophylactically except in certain limited and sharply defined situations. With such matters in mind, the conscientious physician can cut the antibiotic intake of his patients to a sensible minimum level, lower the cost of their medical care, and reduce the occasional hazard and inconvenience associated with the giving of antibiotics.

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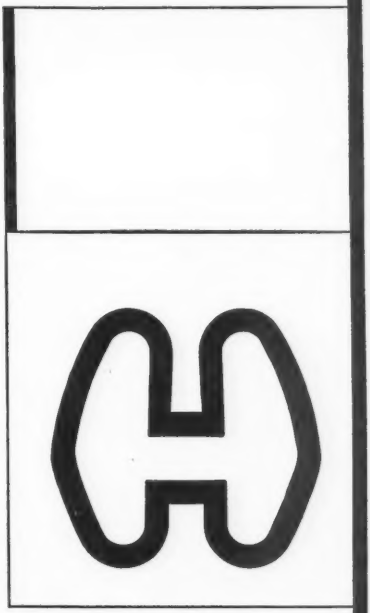

PRESCRIBING INFORMATION

ADMINISTRATION AND DOSAGE: Dosage should be adjusted according to the severity of the condition and the response of the patient.

Most patients should be started on 25 mcg. of 'Cytomel' daily. To increase dosage to recommended maintenance levels for these patients, increments of 12.5 or 25 mcg. may be made in the daily dosage at intervals of one or two weeks. Dosages in the range of 100 mcg. daily, and higher, are well tolerated by many patients.

When starting dosage is 5 mcg. daily (as in myxedema, male infertility, simple goiter and in patients being switched from thyroid, L-thyroxine, or thyroglobulin), increments of 5 or 10 mcg. may be made in the daily dosage at intervals of one or two weeks. When dosage reaches 25 mcg. daily, increase as described above.

'Cytomel' is usually administered in divided doses.

Note: In geriatric patients or in children always start with 5 mcg. daily and adjust dosage in increments no greater than 5 mcg.

Indication	Recommended Starting Dose	Recommended Maintenance Dose
Hypometabolism Mild Hypothyroidism	25 mcg. daily	25-75 mcg. daily (Smaller doses may be fully effective in some patients.)
Myxedema	5 mcg. daily	50-100 mcg. daily
Female Reproductive Disorders	25 mcg. daily	25-50 mcg. daily
Male Infertility (Based on sperm count or sperm motility responses after two to four weeks of treatment at a given dosage level, the daily dosage may be increased by 5 or 10 mcg. If after further treatment the desired response has still not been obtained, the daily dosage may again be increased. Although total daily dosage usually need not exceed 25 mcg., as much as 50 mcg. daily may be used if necessary.)	5 mcg. daily	10-25 mcg. daily
Simple (non-toxic) Goiter	5 mcg. daily	25-75 mcg. daily

SPECIAL CONSIDERATIONS AND CAUTIONS: Tachycardia, excitability, headache, or excessive sweating are signs of overdosage. Medication should be interrupted until the unpleasant symptoms disappear, and then resumed in smaller doses. Since the return to pretreatment status is rapid, 'Cytomel' can usually be resumed at the desired dosage after one to two days.

When a subnormal BMR exists as part of the clinical syndrome of hypometabolism or hypothyroidism, administration in excessive dosage will cause elevation of BMR to levels above normal.

'Cytomel', unlike various forms and fractions of thyroid, will not cause elevation of the blood protein iodine level.

Endogenous thyroid gland function, reflected particularly by I^{131} uptake, may be depressed by 'Cytomel' administration. Depression of this function is most apt to occur with higher dosages (greater than 75 mcg. daily). Experience to date indicates that this effect is not clinically harmful. There have been no unfavorable sequelae in reported instances where 'Cytomel' therapy has been discontinued after depression of I^{131} uptake occurred. In such cases this function has promptly returned to normal after discontinuance of 'Cytomel'.

Since 'Cytomel' is physiologically related to thyroxine, it is not recommended for use in the presence of angina pectoris, in other cardiovascular disorders, or ischemic states. However, if it is used in the presence of such conditions, the starting dosage should never be more than 5 mcg. daily. If dosage is increased, it should be in increments of no more than 5 mcg. daily at approximately two-week intervals.

Hypopituitarism, morphologic hypogonadism and nephrosis should be ruled out before 'Cytomel' is administered.

CONTRAINDICATION: Addison's disease.

FORMULA: Each 'Cytomel' tablet contains 5 mcg. or 25 mcg. of liothyronine (L-triiodothyronine or LT3), as the sodium salt; 25 mcg. of 'Cytomel' is calorigenically equivalent to approximately 1 gr. of thyroid.

AVAILABLE IN TWO DOSAGE STRENGTHS: 25 mcg. (scored) tablets in bottles of 100 and 1000; 5 mcg. tablets in bottles of 100.

Prescribing information adopted Jan. 1961

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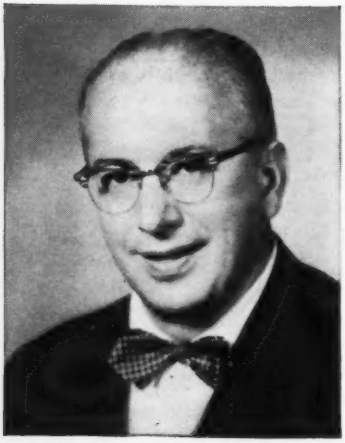
OTOLARYNGOLOGY



Noah D. Fabricant, M.D.
Chicago, Illinois

Noah D. Fabricant is associate editor of the EYE, EAR, NOSE AND THROAT MONTHLY and a contributing editor to the AMERICAN JOURNAL OF MEDICAL SCIENCES. He has published more than 400 articles, essays, editorials, and book reviews, and 13 books, his latest being THIRTEEN FAMOUS PATIENTS (Chilton). He is a member of the American Academy of Ophthalmology and Otolaryngology, and the American Laryngology, Rhinology and Otology Society. Dr. Fabricant wrote on tinnitus in the July CONSULTANT; this month he discusses eye, nose, and ear disturbances that can cause headache.

HEADACHES CAUSED BY DISTURBANCES IN THE EYE, NOSE, OR EAR

While tension and anxiety are probably to blame for most of the headaches we see, the eye, nose, and ear are sometimes the culprits. They may escape blame at first when the patient's attitude suggests tension and anxiety but the emotional state may be the result of headache instead of its cause.

I often see patients referred for relief of persistent headache who are stereotyped caricatures of the typical "nervous wreck." They may sit tensely on the edge of a chair, clasping and unclasping their hands as they describe "unbearable" headache that they suffer "constantly." They may be perspiring when the room temperature is comfortable, or talking too fast in a tremulous voice. "This headache, Doctor . . . I can't stand it. I haven't slept all week; I can't concentrate," and so on.

Sometimes a patient like this *is* a candidate for psychotherapy and a sedative or tranquilizer, but at other times his headache is very real, resulting from a minor visual deficiency or an unsuspected low-grade infection in the sinuses or ears. Persistent pain, even when not severe, can drive a patient to distraction.

To separate somatic and psychic factors, and determine which came first, history and diagnosis are equally im-

portant. Does the headache occur early or late in the day? Has the patient had a cold recently? Has he or she been doing a lot of swimming?

Headache From Ocular Disturbance

Headache from ocular disturbance is due to one or more of the following: refractive errors, muscular imbalance, inflammation, or increased intraocular tension. When the patient recalls that the discomfort originally began, or usually coincides, with a lot of reading, close work, or television viewing, eyestrain should be suspected as the cause.

Eyestrain causes a great many ocular symptoms, ranging from temporary blurring of vision to a dull ache. Ordinarily, pain from eyestrain is mild, but occasionally it is severe. It may be localized or invade every part of the head, from the top of the skull to the nape of the neck. Ocular headaches may be superficial and obvious, or so violent and boring, so full and throbbing, and so persistent that they are mistaken for migraine. The unfortunate victim has an irresistible desire to stop work and close his eyes. Headache due to farsightedness or astigmatism usually is troublesome in the afternoon or evening, following a day's work, especially detailed work requiring close visual inspection. Headache in a farsighted forest ranger is unlikely to be related to his work, of course, but most people's ocular variations are not such useful adaptations.

Imbalance of the small muscles controlling eye movement has a similar effect in causing headache, except that the pain is likely to be at the back of the head.

Headache may result from eyestrain. No one afflicted by obscure headaches should be continued on general medical treatment unless the possibility of eyestrain has been positively eliminated by a careful eye examination. Small refractive errors often give rise to considerable ocular discomfort. Strictly speaking, it is not so much the refractive error that causes trouble as the continuous effort to correct the error. Of course, migraine and pathologic conditions (glaucoma, iritis, and retrobulbar neuritis) do demand medical treatment, and, in the case of migraine, may require psychotherapy as well.

Headache From The Sinuses

Infected sinuses, when drainage is not clearly evident, may be an unsuspected source of headache. Sinus disease usually begins during the terminal stages of the common cold, blending with it so insidiously that most patients fail to distinguish between the nasal infection and the onset of sinusitis. In fact, they may think their cold has "cleared up." In acute frontal sinusitis, headache is a prominent and constant symptom. The confines of the forehead above the eyes and even the eyes themselves are often tender to pressure. Headache associated with frontal sinus disease commonly starts in the morning, gradually becomes worse, and ends toward evening.

In sinus disease—which may involve any of the sinus groups, frontal, maxillary, ethmoid, or sphenoid—headache is significant, but its severity is not a reliable index of the seriousness of infection. Headache is only a symptom, and may be heightened by conditions that increase swelling of the

nasal and sinus mucous membranes: anxiety, excitement, menstruation, cold air, or the mounting effects of alcohol.

Sinus headaches are intensified by stooping, exertion, sneezing, coughing, and sudden movements of the head. The pain may be constant or periodic, and often is sharply localized.

Acute sinus infections are best treated by conservative measures. Rest in bed, application of heat, use of nasal medicaments to enable the patient to breathe freely and to establish sinus drainage, and administration of antibiotics or sulfonamides are all of value. While the infection is being treated, salicylates or other mild pain-relieving drugs usually suffice to relieve pain. Chronic sinus infection will respond to the same measures, but also may require irrigation and gentle suction. While sinusitis is still a major source of headache and other symptoms, improved decongestant and vasoconstricting agents, and antibiotic and sulfa drugs, plus progress in techniques with mechanical measures, have gone a long way toward silencing—permanently—the old cry, "once a sinus, always a sinus."

Ear-induced Head Pain

Few experiences are more intensely disliked than pain in the ear. A dull, steady ache; a sharp, piercing pain, or a rhythmic, throbbing pain commands attention – forcefully and urgently. Fortunately, ear-induced head pain is usually obvious, and its cause is less likely to be mis-diagnosed than eye or sinus trouble.

During the summer the external ear canal is often influenced by hot, humid weather. At this time a host of microorganisms find the ear canal an especially attractive locale for growth and multiplication, and thereby cause trouble. Many infections are activated by excessive perspiration and by swimming in polluted water.

Three of the most annoying types of external ear canal disease include purulent infection, fungus infection, and eczematous reaction. In the case of a well-developed furuncle, the pain and accompanying headache soon attain heights out of all proportion to the limited size of the infection. Pain often becomes so severe as to interfere with sleep. Movements of the jaw while eating, talking, or yawning aggravate the pain. The appearance of a swelling behind the ear often alarms the patient—unless he is reassured by his physician that it is not due to a mastoid infection.

Fortunately, instituting prompt, energetic therapeutic measures ensures a cure. Application of heat to the affected ear, and appropriate local and systemic antibiotic or chemotherapeutic medication, will ordinarily promote a rapid cure, but in the meantime the patient will demand relief of pain, which can usually be obtained by analgesics. If this does not provide symptomatic relief, it may be necessary to use a sedative, such as phenobarbital.

Generally speaking, suppressing headache by the use of salicylates or other measures is of only temporary symptomatic value when pain is caused by eye, nose or ear disturbances. These must be diagnosed and cured to bring lasting relief.

SPECIAL FEATURE

Morton Klein, Ph.D.
Temple University

Morton Klein is Professor of Microbiology at Temple University School of Medicine. He received his Ph.D. in microbiology from the University of Pennsylvania, and has been on the teaching staffs of the medical schools of the University of Pennsylvania, University of Chicago, and Jefferson Medical School. He is a Fellow of the American Association for the Advancement of Science and the New York Academy of Sciences. His current research interests are viral chemotherapy and the relationship between human and animal virus infections, with special interest in "natural" resistance of species to viral infection.

HOW DO VIRUSES MULTIPLY?

In 1935, Dr. Wendell Stanley, at the Rockefeller Institute at Princeton, made a most arresting observation. He published a paper reporting isolation of a crystalline protein possessing the properties of tobacco mosaic virus. In this and subsequent studies, Stanley showed that the parasite causing the disease was a crystalline protein 300-millimicrons by 15-millimicrons. It contained just two substances, ribonucleic acid (RNA) and protein, and was completely devoid of the basic equipment, such as enzymes, essential to all known living cells. This discovery had a great impact on medicine because it was the first major insight into the nature of the virus particle and led to intensive research on the nature of viruses causing human infections. As we shall see, these studies on the nature of the viral particle have helped clarify the following characteristics of viruses and virus disease:

1. Viruses have an enormous capacity to cause acute infections, which in over 99.9% of the cases are benign and self-limiting.

2. They cause cancer in many animals, and there is currently intense speculation about their potential role in causing human cancer.

3. Some viruses have an unusual ability to remain latent in the body for long periods of time. The virus of Herpes simplex, for example, occurs as a primary infection in childhood, disappears with no trace of active virus in the body, but may recur at irregular intervals as the fever blister, with the production of infectious virus.

4. The traditional defenses in our recovery from infection – phagocytes and antibodies – apparently *do not* play a significant role in our *recovery* from viral infections, although antibodies are of course important in our *immunity* to viral infections.

5. Viruses are completely resistant to all our chemotherapeutic agents.

The First Clue

For many years prior to Stanley's discovery, an air of mystery had surrounded these filtrable parasites, the viruses. The first was discovered in 1892, when a plant pathologist named Iwanowski studied tobacco mosaic virus disease, and in the course of his studies ground up and filtered some infected leaves. The filter held back all living parasites. He saw nothing and grew nothing from this filtrate and, according to the official definition of the time, the material was sterile. But then he did this: he took some of the apparently sterile material, rubbed it on the surface of a tobacco plant, and the plant came down with the infection. Neither Iwanowski nor anyone living at the time could possibly interpret this strange observation, though it was apparent that something acting like a living parasite was capable of multiplying in the cells of the tobacco plant.

In 1899, a similar observation was made with a disease of cattle – hoof and mouth disease – and in 1901 with yellow fever in humans. Thus, at the turn of the century we knew we were surrounded by a new kind of parasite whose nature was totally unknown. It was invisible with the light microscope, incapable of growing in the available nutritional media, and its presence could be detected only because it caused infections in plants, in animals, and in man.

Biologists believed they knew, until the advent of these filtrable parasites, how living things should multiply. Living cells had a nucleus, cytoplasm, a cell wall, and enzymes to utilize nutrients and carry out the necessary cellular syntheses; the cell multiplied by binary fission. However, all attempts to make these new, invisible particles behave like typical living cells failed. Filtrates containing the active agents were exposed to every known nutritional substance, under conditions optimum for cellular growth, but no one ever obtained even a metabolic quiver from these infectious filtrates. They floated inert and indifferent in this rich organic milieu, coming to life only when exposed to their specific host cell.

After Stanley's discovery in 1935, it was shown that the simple structure characteristic of the tobacco mosaic virus was a basic property of many human viruses for the coxsackie, Echo and polioviruses: all contained only RNA and protein. There were some minor variations on this theme. Adenoviruses contained desoxyribonucleic acid (DNA) and protein. Certain viruses, e.g. influenza, contained in addition lipid and polysaccharide. *In no case did any virus possess the enzymes needed to function as a living cell.* It was thus clear that a totally new concept of a living thing had to be developed to explain the multiplication of a crystal that contained only nucleic acid and protein.

The Key to the Mystery

The key to the mystery of viral multiplication lay in the discovery of the role of desoxyribonucleic acid (DNA) in carrying the genetic code of all living things. For many years heredity was discussed in terms of the classic morphological entities, the chromosomes, containing their hypothetical units, the genes. Though these genes obviously resided in the nucleus, no

one knew whether chemically they were protein, nucleic acid, or combinations of both. The genetic role of DNA was first demonstrated in 1944 in a classical experiment done with pneumococci. One could extract DNA from capsulated pneumococci, and this purified DNA would transmit to another pneumococcus, devoid of the ability to synthesize a capsule, this new genetic trait, the ability to synthesize the capsular polysaccharide. Subsequently, it was shown that other properties of a cell, undoubtedly all properties, could be transferred using only DNA. The chemical nature of the DNA has since been studied in considerable detail. Its basic structure is a polynucleotide in the form of paired, intertwined, identical chains. These paired chains are made up of four different chemical units, nucleotides, each repeated many millions of times on the chain in varying sequences. Millions of chemical patterns or codes can be made from these four basic nucleotide structures. *A gene is thus a chemical code, a sequence of a few nucleotides, and the millions of nucleotides in the chain allow for the coding of many thousands of genes.*

The ability to undergo mutation is a characteristic of all living cells, and we now know *a change in one or many of these nucleotides may result in a mutation* – provided the cell is not killed. In the course of cell division, the introduction of a nucleotide in the wrong place in the chain may cause a spontaneous mutation. Irradiation may damage the DNA molecule leading to mutations, as may a variety of chemical substances. The fundamental observation is this: *A modification in the nucleic acid of a cell can lead to a genetic change resulting in a new and distorted pattern of cellular metabolism. The introduction of a foreign fragment of nucleic acid is one way of achieving this genetic change.*

Let us consider one more experiment. One can take one of several viruses, e.g. poliovirus and gently disrupt the virus by separating the protein from the nucleic acid portion. If one now injects intracerebrally into a mouse a chemical solution, the poliovirus nucleic acid, the animal becomes paralyzed, dies, and one can isolate the crystals of the complete infectious poliovirus from the brain.

The following picture of viral multiplication can now be drawn. The role of the protein coat is only to protect the parasitic but labile nucleic acid and obtain its entry into the cell. Pure viral nucleic acid outside of the cell is readily inactivated even by normal blood. The protein coat also gives a virus its cellular specificity. A virus' ability to invade only certain cells, results from this limited ability of the protein coat to enter cells. Once inside the cell, the protein coat is discarded, the nucleic acid is released, either DNA or RNA. Some viruses contain DNA, others RNA, no virus both. Just why this variation in nucleic acid exists is not understood, but either DNA or RNA can carry out the parasitic function of the virus. The viral nucleic acid either modifies the DNA of the host cell, in effect causing a mutation or series of mutations, or directly substitutes its own nucleic acid for part of the host nucleic acid. In either event the synthetic activity of the cell is modified, and under the direction of the viral nucleic acid, the cell is forced to synthesize infectious viral particles. *This genetic modification of the cell may vary in intensity from barely detectable changes in*

cellular metabolism, not sufficient to interfere with cell division, to dramatic changes in cell metabolism leading to the prompt synthesis of thousands of viral particles and death of the cell.

What We Now Know

With this description of viral growth we can now understand the broad and unusual pattern of viral activity.

1. We know why virus particles are so small. They do not need the total apparatus of a living cell.

2. We know why virus particles can multiply only in the presence of living cells. Their essential nutritional need is the total metabolic apparatus of a living cell. They must "take over" the cell because, devoid of their own enzymes, they cannot utilize any nutrients.

3. We understand why the true viruses are resistant to the available chemotherapeutic agents. These therapeutic agents act by either denying a bacterial cell a needed nutritional component or directly inhibiting the activity of some of their enzymes. Since viruses have no independent metabolism, there is nothing that the chemotherapeutic agent can inhibit. The so-called "large viruses," the agents of trachoma, psittacosis, lymphogranuloma venereum are effectively inhibited by broad-spectrum antibiotics, but they are not true viruses. They contain, like bacteria, both DNA and RNA, they are capable of considerable independent metabolic activity and apparently divide by binary fission, though only intracellularly. These are obviously not "genetic parasites."

4. The concept of a viral particle as a biological mutagenic agent indicates its role in causing cancer. If the nucleic acid of the viral particle causes only a minimal mutational effect, the metabolism of the cell is distorted only slightly, the cell still continues to divide, though the modification in the genetic structure of the cell may have resulted in a malignant change. As we have previously noted, viruses have been demonstrated as a cause of cancer unequivocally only in some animals. A virus theory of human malignancy is based essentially on an analogy—viruses cause a broad range of familiar malignant changes in some animals, why not man?

5. The concept of viral latency can also be explained in terms of infectious nucleic acid. The viral nucleic acid may enter a cell, move to the cell nucleus and fail to initiate any mutational change in the cell. However, the viral nucleic acid may be incorporated into the cell genome, and this foreign fragment of viral nucleic acid may be synthesized along with the host nucleic acid. The cell divides in a totally normal fashion, though always synthesizing this fragment of viral nucleic acid, which, though potentially active, fails to express itself phenotypically. There is no change in the functioning of the cell. However, under certain conditions this viral fragment of nucleic acid may be activated and effect its mutational changes with cellular synthesis of active virus. This sequence of events may thus explain the latency observed with the recurrent fever blister of Herpes simplex where there is a variety of activating factors, fever, etc. One may also suggest that chemical carcinogens may frequently function as activators of latent viruses.

6. We now can understand why neither phagocytes (which do not

effectively destroy viruses) nor antibodies (whose almost total absence in agammaglobulinemia does not retard the rate of recovery from viral infections) may not be necessary for *recovery* from viral infections. As we have noted above viruses probably can invade only certain cells because of the need for a specific affinity between each virus' protein coat and some receptor sites on the host cell. Thus each virus species causes a specific illness because it has a limited crop of available cells that it can invade and destroy. If the available susceptible cells are destroyed the illness is automatically terminated without benefit of phagocytes or antibody. Viruses cannot linger as do many bacteria in a spot of blood or pus. They need an immediate and continuing supply of susceptible cells. When these cells are destroyed the virus has no place to go and the infection is terminated.

The idea of a viral particle as essentially an invading bit of nucleic acid, acting as a parasitic gene or biological mutagen, is the simple unifying concept. The ability of the total of all viruses to change almost any cell in a variety of ways explains the broad range of viral activity. The inability of any single virus to invade and destroy more than a limited number of cells explains the typically benign course of most viral infections. The possible role of viruses in the causation of human malignancy, the more intimate biochemical details of viral multiplication and the problems of therapy of viral infections remain the major areas of exploration in the field of virology.

THORAZINE®
brand of chlorpromazine

PRESCRIBING INFORMATION

Tranquilizer • Antiemetic • Potentiator

The wide diversity of clinical applications in which 'Thorazine' is valuable, as either a specific or an adjuvant, is due to its three fundamental clinical properties: (1) its capacity to alleviate anxiety, tension and agitation without dulling mental acuity, (2) its ability to potentiate sedatives, narcotics and anesthetics, and (3) its profound antiemetic effect.

The tranquilizing effect of 'Thorazine' accounts for its usefulness in somatic conditions where emotional stress is a factor, as well as in mental and emotional disturbances *per se*.

INDICATIONS

The value of 'Thorazine' is established in the following conditions:

Moderate to severe mental and emotional disturbances of everyday practice, particularly those disturbances marked by agitation, tension, apprehension, excitement, or anxiety.

Somatic conditions complicated by emotional stress, such as arthritis, tuberculosis, severe tension headaches, gastrointestinal disorders, dermatologic conditions, status asthmaticus and severe asthma.

Hospitalized psychiatric patients, to control agitation, dispel delusions and hallucinations, and at the same time to restore or increase the patient's capacity to respond to psychotherapy.

Nausea, vomiting and hiccups, with dramatic results in severe and refractory cases.

Acute or chronic alcoholism, to control agitation, delirium tremens, and nausea and vomiting.

Cancer, as an adjuvant, to control apprehension, suffering due to pain, and nausea and vomiting.

Intractable pain, to reduce suffering and to potentiate narcotics or sedatives.

Obstetrics, as an adjuvant, to control apprehension, pain, and nausea and vomiting. 'Thorazine' allows a reduction in the amounts of the drugs ordinarily used in obstetrical management, thus lessening the risk of respiratory depression in mother and infant.

Surgery, as an adjuvant, to control anxiety and apprehension, pain, and nausea and vomiting; and to reduce by potentiation the amounts of narcotics, sedatives and anesthetics needed.

ADULT DOSAGE AND ADMINISTRATION

Dosage should always be adjusted to the response of the individual and the severity of the condition. It is important to increase dosage until symptoms are controlled or side effects become troublesome.

Mental and Emotional Disturbances of Everyday Practice – Depending on severity, *starting oral dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. After a day or two, dosage may be increased by increments of 20 mg. to 50 mg. daily, at semiweekly intervals (increase should be more gradual in emaciated or senile patients) until achieving maximum clinical response. Continue dosage at this level for at least two weeks: then it can usually be reduced to a maintenance level. A daily dosage of 200 mg. is "average," but in some cases, such as discharged mental patients, daily dosages as high as 800 mg. may be necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If necessary, and if no hypotension occurs, repeat the initial dose in one hour. Subsequent dosages should be oral, starting at 25 mg. to 50 mg. t.i.d.

Somatic Conditions Complicated by Emotional Stress—*Starting oral dosage* is 10 mg. to 25 mg. t.i.d. or q.i.d. Increase gradually by 10 mg. to 25 mg. increments at semiweekly or weekly intervals. *Starting intramuscular dosage* is 25 mg. (1 cc.), repeated after one hour if necessary and if no hypotension occurs.

Hospitalized Psychiatric Patients – ***Acutely agitated, manic, or disturbed patients:*** *Starting intramuscular dose* is 25 mg. (1 cc.). If no marked hypotension occurs, an additional 25 mg. to 50 mg. injection may be given after one hour. Subsequent intramuscular dosages may be increased gradually over a period of several days – even up to 400 mg. q4-6h in exceptionally severe cases – until the patient is controlled. (In elderly or emaciated patients the dosage should be increased more slowly than in other patients.) Usually the patient becomes quiet and cooperative within 24 to 48 hours after the initial dose, at which time oral doses may gradually be substituted for intramuscular doses (mg. for mg. or higher). Even if control is not complete, oral doses may gradually replace intramuscular doses. During this period, oral dosage should be increased rapidly until the patient is calm. Usually an *oral dose* of 500 mg. a day is sufficient but, if necessary, the dosage may be gradually increased still further to 2,000 mg. a day or higher. ***Less acutely agitated patients:*** *Starting oral dose* is 25 mg. t.i.d. Subsequently, increase the amount gradually until an effective dosage is reached – usually 400 mg. daily is sufficient. ***Duration of therapy:*** It is important to determine the optimal dosage regimen and to continue treatment long enough for maximum clinical response. Maximum improvement is sometimes not apparent until after weeks or even months of therapy.

Nausea and Vomiting – *Starting oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n., and may be increased if necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If no hypotension occurs subsequent doses of 25 mg. to 50 mg. q3-4h, p.r.n., may be given until vomiting is checked. Then replace intramuscular administration with oral. *Starting rectal dosage* is one 100 mg. suppository q6-8h, p.r.n. In some patients, one-half this dose may be sufficient.

Hiccups – *Starting oral dosage* is 25 mg. to 50 mg. t.i.d. or q.i.d. If after 2-3 days symptoms persist, *an intramuscular dosage* of 25 mg. to 50 mg. (1-2 cc.) may be used. *Use intravenous administration* only when symptoms still persist. By slow infusion, 25 mg. to 50 mg. (1-2 cc.) should be administered in 500 cc. to 1,000 cc. of physiologic saline solution, with the patient kept flat in bed. Follow blood pressure closely.

Alcoholism – ***Severely agitated patients:*** *Starting intramuscular dose* is 25 mg. to 50 mg. (1-2 cc.). Repeat initial dose if necessary and if no hypotension occurs. Start subsequent oral dosages at 25 mg. to 50 mg. t.i.d. ***Agitated but manageable patients:*** *Starting oral dose* is 50 mg., followed by 25 mg. to 50 mg. t.i.d. ***Ambulatory patients with withdrawal symptoms or sober chronic alcoholics:*** *Starting oral dose* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Patients in a stuporous condition should be allowed to sleep off some of the effects of the alcohol before 'Thorazine' is administered.

Cancer and Pain – ***Severe pain:*** *starting intramuscular dosage* is 25 mg. (1 cc.) b.i.d. or t.i.d. ***Milder pain:*** starting oral *dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Because 'Thorazine' potentiates their action, reduce the dosage of narcotics or sedatives to ¼ to ½ of the pre-'Thorazine' level.

Obstetrics – *Intramuscular dose* in labor and delivery is 12.5 mg. to 25 mg. (0.5-1 cc.), administered when dilation of the cervix reaches 3 to 5 centimeters or when strong labor is established. At the same time (but not mixed in the syringe with 'Thorazine'), ¼ to ½ the usual dose of a narcotic or sedative and, if desired, 0.4 mg. of scopolamine may be administered. Depending upon blood pressure, respiration and the general condition of the patient, the initial 'Thorazine' dose (alone or with reduced amounts of the other agents) may be repeated in 3 to 5 hours if necessary.

Surgery (Adults) – ***Preoperatively,*** *oral dose* is 25 mg. to 50 mg., 2 to 3 hours before the operation. *Intramuscular dose* is 12.5 mg. to 25 mg. (0.5-1 cc.), 1 to 2 hours before the operation. ***During surgery*** 'Thorazine' should be administered only if needed to control nausea and vomiting, retching, hiccups, or other acute symptoms. *Intramuscular dose* is 12.5 mg. (0.5 cc.), repeated in ½ hour if necessary and if no hypotension occurs.

Intravenous dose should be no more than 2 mg. per fractional injection, with injections at not less than 2-minute intervals. Also, it should not exceed 25 mg. 'Thorazine' should be diluted to 1 mg./cc. (1 cc. mixed with 24 cc. of physiologic saline solution). ***Postoperatively,*** *oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n. *Intramuscular dosage* is 12.5 mg. to 25 mg. (0.5-1 cc.), repeated in one hour if necessary and if no hypotension occurs.

PEDIATRIC DOSAGE AND ADMINISTRATION

Nausea and Vomiting, Behavior Disorders and Pain – *Oral dosage* is on the basis of ¼ mg./lb. of body weight q4-6h, until symptoms are controlled (i.e., for 40 lb. child–10 mg. q4-6h). Calculate 'Thorazine' Syrup dosage at 10 mg./5 cc. tsp. *Rectal dosage* is on the basis of ½ mg./lb. of body weight q6-8h, p.r.n. (i.e., for 20-30 lb. child–half of a 25 mg. suppository q6-8h). *Intramuscular dosage* is on the basis of ¼ mg./lb. of body weight q6-8h, p.r.n. In children up to 5 years (or 50 lbs.)–not over 40 mg./day. In children 5-12 years (or 50-100 lbs.)–not over 75 mg./day.

Pain–Because 'Thorazine' potentiates the action of narcotics and sedatives, reduce the dosage of these agents to ¼ to ½ of the pre-'Thorazine' level.

Behavior Disorders–In severe cases, 50-100 mg. daily has been used and, in older children, 200 mg. or more daily may be required.

Surgery (Children) – ***Preoperatively,*** dose is on the basis of ¼ mg./lb. of body weight given either orally 2 to 3 hours before the operation, or intramuscularly 1 to 2 hours before. ***During surgery,*** the dose is on the basis of ⅛ mg./lb. of body weight, repeated in ½ hour if necessary and if no hypotension occurs. The intravenous dose should be no more than 1 mg. per fractional injection, with injections at not less than 2-minute intervals. Intravenous dosage during surgery should not exceed recommended intramuscular dosage and should always be diluted to 1 mg./cc. ***Postoperatively,*** dosage is on the basis of ¼ mg./lb. of body weight, either orally q4-6h, p.r.n., or intramuscularly, a single dose repeated in one hour if necessary and if no hypotension occurs.

NOTES ON PARENTERAL ADMINISTRATION

Except for acute ambulatory cases, parenteral administration should generally be reserved for bedfast patients. Parenteral administration should always be made with the patient lying down and remaining so for at least ½ hour afterward because of possible hypotensive effects. The injection should be given *slowly, deep* into the upper outer quadrant of the buttock. If irritation and pain at the site of injection are problems, dilution of 'Thorazine' Injection with physiologic saline solution or 2% procaine solution may be helpful. Subcutaneous administration is not advisable, and care should be taken to avoid injecting undiluted 'Thorazine' Injection into a vein. Intravenous administration is recommended only for severe hiccups and surgery.

Because contact dermatitis has been reported, avoid getting the solution on hands or clothing.

SIDE EFFECTS

The drowsiness caused by 'Thorazine' may be unwanted in some patients. It is usually mild to moderate and disappears after the first or second week of therapy. If, however, drowsiness is troublesome, it can usually be controlled by lowering the dosage or by administering small amounts of dextro amphetamine.

Other side effects that have been reported occasionally are dryness of the mouth, nasal congestion, some constipation, miosis in a few patients and, very rarely, mydriasis. Mild fever (99°F.) may occur occasionally during the first days of therapy with large intramuscular doses. During 'Thorazine' therapy some patients have an increased appetite and gain weight. Usually these patients reach a plateau beyond which they do not gain further weight.

CAUTIONS

Jaundice: In the more than 14 million patients who have been treated with 'Thorazine' in the United States, the incidence of jaundice–regardless of indication, dosage, or mode of administration–has been low. Few cases have occurred in less than one week or after six weeks. Jaundice due to 'Thorazine' is of the so-called "obstructive" type; is without parenchymal damage; and is usually promptly reversible upon the withdrawal of 'Thorazine'. Because detailed liver function tests of 'Thorazine'-induced jaundice give a picture which mimics extrahepatic obstruction, exploratory laparotomy should be withheld until sufficient studies confirm extrahepatic obstruction.

Agranulocytosis: Agranulocytosis, although rare, has been reported in patients on 'Thorazine' therapy. Patients receiving 'Thorazine' should be observed regularly and asked to report at once the sudden appearance of sore throat or other signs of infection. If white blood counts and differential smears give an indication of cellular depression, the drug should be discontinued, and antibiotic and other suitable therapy should be instituted. Because most reported cases have occurred between the fourth and the tenth weeks of treatment, patients on prolonged therapy should be observed particularly during that period.

A moderate suppression of total white blood cells is sometimes observed in patients on 'Thorazine' therapy. If not accompanied by other symptoms, it is not an indication for discontinuing 'Thorazine'.

Potentiation: 'Thorazine' prolongs and intensifies the action of many central nervous system depressants, such as barbiturates and narcotics. Consequently, it is advisable to stop administration of such depressants before initiating 'Thorazine' therapy. Later the depressant agents may be reinstated, starting with low doses, and increasing according to response. Approximately ¼ to ½ the usual dosage of such agents is required when they are given in combination with 'Thorazine'. (However, 'Thorazine' does not potentiate the anticonvulsant action of barbiturates. In patients who are receiving anticonvulsants, the dosage of these agents–including barbiturates–should not be reduced if 'Thorazine' is started. Rather, 'Thorazine' should be started at a very low dosage and increased, if necessary.)

Hypotensive Effect: Postural hypotension and simple tachycardia may be noted in some patients. In these patients, momentary fainting and some dizziness are characteristic and usually occur shortly after the first parenteral dose, occasionally after a subsequent parenteral dose–very rarely after the first oral dose. In most cases, prompt recovery is spontaneous and all symptoms disappear within ½ to 2 hours with no subsequent ill effects. Occasionally, however, this hypotensive effect may be more severe and prolonged, producing a shock-like condition. In consideration of possible hypotensive effects, the patient should be kept under observation (preferably lying down) for some time after the initial parenteral dose. If, on rare occasions, hypotension does occur, it can ordinarily be controlled by placing the patient in a recumbent position with head lowered and legs raised. If it is desirable to administer a vasoconstrictor, 'Levophed' and 'Neo-Synephrine'★ are the most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Antiemetic Effect: The physician should always bear in mind that the antiemetic effect of 'Thorazine' may mask signs of overdosage of toxic drugs and may obscure diagnosis of conditions such as intestinal obstruction and brain tumor.

Dermatological Reactions: Dermatological reactions have been reported. Most have been of a mild urticarial type, suggesting allergic origin. Some of them appear to be due to photosensitivity, and it is advisable that patients on 'Thorazine' avoid undue exposure to the summer sun.

Neuromuscular Reactions: With very large doses of 'Thorazine', as frequently used in psychiatric cases over long periods, there have been a few patients who have exhibited neuromuscu-

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★'Levophed' and 'Neo-Synephrine' are the trademarks (Reg. U.S. Pat. Off.) of Winthrop Laboratories for its brands of levarterenol and phenylephrine respectively.

lar reactions (extrapyramidal symptoms) which closely resemble parkinsonism. Such symptoms are reversible and usually disappear within a short time after the dosage has been decreased or the drug withdrawn. These neuromuscular reactions can also be controlled by the concomitant administration of standard anti-parkinsonism agents.

Lactation: Moderate engorgement of the breast with lactation has been observed in female patients receiving very large doses of 'Thorazine'. This, however, is a transitory condition which disappears on reduction of dosage or withdrawal of the drug.

CONTRAINDICATIONS

In comatose states due to central nervous system depressants (alcohol, barbiturates, narcotics, etc.), and also in patients under the influence of large amounts of barbiturates or narcotics.

AVAILABLE

Tablets, 10 mg., 25 mg., 50 mg. and 100 mg., in bottles of 50, 500 and 5000; 200 mg., for use in mental hospitals, in bottles of 500 and 5000. (Each tablet contains chlorpromazine hydrochloride, 10 mg., 25 mg., 50 mg., 100 mg., or 200 mg.)

Ampuls, 1 cc. and 2 cc. (25 mg./cc.), in boxes of 6, 100 and 500. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 6 mg.)

Multiple-dose Vials, 10 cc. (25 mg./cc.), in boxes of 1, 20 and 100. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 1 mg. Contains benzyl alcohol, 2%, as preservative).

Spansule® capsules, 30 mg., 75 mg., 150 mg. and 200 mg., in bottles of 30, 250 and 1500; also 300 mg., in bottles of 30 and 1500. (Each 'Spansule' capsule contains chlorpromazine hydrochloride, 30 mg., 75 mg., 150 mg., 200 mg., or 300 mg.)

Syrup, 10 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. (Each 5 cc. contains chlorpromazine hydrochloride, 10 mg.)

Suppositories, 25 mg. and 100 mg., in boxes of 6. (Each suppository contains chlorpromazine, 25 mg. or 100 mg.; glycerin, glyceryl monopalmitate, glyceryl monostereate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids, lecithin.)

Concentrate (for hospital use), 30 mg./cc., in 4 fl. oz. bottles, packages of 12 and 36; and in 1 gal. bottles. (Each cc. contains chlorpromazine hydrochloride, 30 mg.)

Prescribing information adopted January, 1961

COMPAZINE®
brand of prochlorperazine

PRESCRIBING INFORMATION

Antiemetic • Tranquilizer

'Compazine' provides a beneficial calming effect and prompt antiemetic action with unusual freedom from drowsiness and depressing effect. Clinical experience in several million patients has shown 'Compazine' to be promptly effective in low dosage, with minimal side effects in the dosage range recommended for everyday practice.

INDICATIONS

*1. **Anxiety, tension, agitation,*** confusion, chronic alcoholism and behavior disorders in children.

*2. **Emotional stress associated with somatic conditions*** such as g.i. disorders, cardiovascular conditions, hypertension, menopause, premenstrual tension, neurodermatitis, arthritis, asthma, cancer, tuberculosis and tension headache.

*3. **Nausea and vomiting of widely varying causes*** such as pregnancy, postoperative conditions, viral gastroenteritis and other infectious conditions, irradiation therapy and motion sickness. In most patients, relief is provided within a short time after one oral dose.

*4. **In surgery and obstetrics*** to prevent or control: (a) nausea, vomiting and retching; and (b) fear, tension and restlessness.

*5. **In psychiatry*** to control agitation, anxiety, tension and confusion that may be seen in psychotic states.

ADMINISTRATION AND USUAL DOSAGE

Dosage should be determined according to the severity of the condition and the response of the patient. It is important to begin therapy with the lowest recommended dosage. In hospitalized patients or those under adequate supervision, higher doses may be indicated.

USUAL ADULT DOSAGE

Tablets: The usual starting dosage is 5 mg. three or four times daily. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. Dosage over 40 mg. daily should be used only in resistant cases.

Spansule® sustained release capsules: The usual starting dosage is one 15 mg. 'Spansule' capsule taken upon arising, or one 10 mg. 'Spansule' capsule in the morning and evening. Some patients may subsequently require dosage increased to one 30 mg. capsule in the morning. Dosage over 40 mg. daily should be used only in resistant cases. (B.i.d. dosage of the 30 mg. capsule should be limited to severe cases.)

Dosage recommendations for other oral forms of 'Compazine' may be applied to 'Compazine' *Spansule* capsules on the basis of the total daily dose in milligrams. (For example: one 15 mg. 'Compazine' *Spansule* capsule replaces 5 mg. 'Compazine' Tablets, t.i.d.) All strengths have the same *duration* of action. They differ only in *intensity* of therapeutic effect.

In "morning sickness" of pregnancy, one 'Compazine' *Spansule* capsule taken before retiring affords antiemetic activity throughout the night and into the morning, thus protecting against "morning sickness."

The 15 mg. 'Compazine' *Spansule* capsule is ideal for once-a-day administration. The 10 mg. 'Compazine' *Spansule* capsule is ideal for twice-a-day (q12h) administration.

Syrup: 5 mg. to 10 mg. (1 to 2 teaspoonfuls) three or four times daily.

Suppositories: Usual dosage in adults is one 25 mg. 'Compazine' Suppository twice daily.

Injection: Total parenteral dosage in 24 hours should not exceed 40 mg.

For intramuscular administration, an initial dose of 5 mg. to 10 mg. (1 to 2 cc.) of 'Compazine' Injection should be injected *deeply* into the upper outer quadrant of the buttock. Repeat, if necessary, at intervals of 3 to 4 hours. Pain at the site of injection has not been a problem. ***For intravenous administration,*** see surgery section. Dilution is not required. ***Subcutaneous administration*** is not advisable because of local irritation.

It is recommended that 'Compazine' Injection not be mixed with other agents in the syringe.

Dermatitis due to contact with 'Compazine' has not been a problem. However, it is recommended that nurses or others giving frequent injections take precautions to avoid getting the solution on their hands or clothing.

'Compazine' Injection should be protected from light, since exposure may cause discoloration. Slight yellowish discoloration will not significantly alter the potency or therapeutic efficacy. However, if markedly discolored, the solution should be discarded.

IN SURGERY (Adults)

ROUTE	DOSAGE
preoperatively	
Intramuscular injection	5 mg. to 10 mg. (1-2 cc.)

1 to 2 hours before induction of anesthesia. Repeat once in 30 minutes if necessary.

ROUTE	DOSAGE
Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

15 to 30 minutes before induction of anesthesia.

Intravenous infusion	20 mg. (4 cc.) per liter of isotonic solution

Add to I.V. infusion 15 to 30 minutes before induction. Repeat once if necessary.

during surgery

Intramuscular or Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

When needed to control acute symptoms. Repeat once if necessary.

postoperatively

To prevent anxiety, nausea, vomiting, or emergence excitement, add to I.V. infusion: 20 mg. (4 cc.) per liter of isotonic solution.

For immediate control of acute nausea, vomiting, retching, or emergence excitement, inject 5 mg. to 10 mg. (1-2 cc.), I.V. or I.M. Repeat once if necessary.

IN OBSTETRICS

'Compazine' dosage should be adjusted to the individual patient and her condition in accordance with the general use of the drug (i.e., 5 mg. to 10 mg. per dose; 15 mg. to 40 mg. per day). The following dosage suggestions should prove satisfactory for the majority of obstetric patients.

To relieve anxiety or prevent vomiting during the first stage of labor, the usual dosage is 10 mg. of 'Compazine' by intramuscular injection. As labor progresses, or if it is prolonged, subsequent 10 mg. doses may be administered as needed. The total daily dose need rarely exceed 30 mg.

To control postpartum anxiety or nausea and vomiting, the usual total daily dose of 'Compazine' is 15 mg. to 30 mg. administered orally or intramuscularly.

NOTE: 'Compazine' has no clinically significant potentiating effect on narcotics, anesthetics, or sedatives. However, because the 'Compazine' patient is calm and relaxed, it is sometimes possible to produce satisfactory analgesia with less than the customary amounts of these agents. This lack of potentiating effect also minimizes the risk of intensifying or prolonging the effect of residual anesthetics and other depressant agents used in surgery or labor and delivery.

As with intravenous administration of any surgical or obstetric adjuvant, the increased possibility of hypotension should be kept in mind if 'Compazine' is administered by either intravenous injection or infusion.

USUAL CHILDREN'S DOSAGE

It is important always to use the lowest effective dosage, because as dosage is raised the possibility of side effects increases. There have been occasional cases of neuromuscular reactions (extrapyramidal symptoms) in children. These have been transitory and reversible.

Nausea and vomiting are usually controlled during the first day of therapy. Therefore more than one day's therapy is seldom necessary.

Weight	Dosage	Not to exceed
Under 20 lbs.	not recommended	
20-29 lbs.	2.5 mg. once or twice a day	7.5 mg. per day
30-39 lbs.	2.5 mg. b.i.d. or t.i.d.	10.0 mg. per day
40-85 lbs.	2.5 mg. t.i.d. or 5 mg. b.i.d.	15.0 mg. per day

For behavior disorders, dosage may be increased gradually, if necessary, within the following daily limits:

2 to 6 years of age: Total daily dose should not exceed 20 mg.
6 to 12 years of age: Total daily dose should not exceed 25 mg.

For rapid control of nausea and vomiting or behavior disorders:

Injection: For children under 12 years of age, each dose should be calculated on the basis of 0.06 mg. of 'Compazine' per pound of body weight and should be administered by deep intramuscular injection. For example, a 40-pound child would receive an injection of 2.5 mg. (0.5 cc.). Control is usually obtained with a single dose.

'COMPAZINE' IN PSYCHIATRY

'Compazine' is indicated for control of agitation, anxiety, tension and confusion that may be seen in such conditions as schizophrenias; manic-depressive states, manic phase; severe personality disorders; involutional psychoses; degenerative conditions; and senile psychoses.

ADULTS

Oral psychiatric dosage: ***In relatively mild conditions,*** as may be seen in private psychiatric practice or on outpatient clinics, the suggested starting dosage is 5 mg. t.i.d. or q.i.d. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. ***In moderate or severe conditions,*** when patients are either hospitalized or under adequate supervision, the suggested starting dosage is 10 mg. t.i.d. or q.i.d. Dosage should be increased gradually until symptoms are controlled or side effects become bothersome. Experience has shown that when dosage is increased gradually (by small increments every two or three days) side effects either do not occur or are easily controlled.

Some patients will obtain satisfactory results on 50 mg. to 75 mg. of 'Compazine' daily. In more severe disturbances, the optimum dosage in most patients is 100 mg. to 150 mg. daily. With oral administration, response ordinarily becomes evident within a day or two. Longer periods of treatment are usually required before maximal improvement is obtained.

I.M. psychiatric dosage: For immediate control of severely disturbed adult patients, an initial dose of 10 mg. to 20 mg. (2-4 cc.) should be injected deeply into the upper outer quadrant of the buttock. If necessary, this dose should be repeated every 2 to 4 hours to gain control of the patient. Patients often respond shortly after the first injection. In resistant cases, the initial dose may be repeated hourly. More than three or four doses are seldom necessary. If, in rare cases, parenteral medication is indicated over a prolonged period, 10 mg. to 20 mg. (2-4 cc.) at 4- to 6-hour intervals is the usual dosage. Pain and irritation at the site of injection have rarely been encountered and some patients have been given the drug intramuscularly for periods of several weeks. After control is achieved by intramuscular administration, most patients can be switched to an oral form of the drug at the same dosage level or higher.

CHILDREN *(2 to 12 years)*

Oral psychiatric dosage: The suggested children's starting dosage in psychiatry is 2.5 mg. (½ teaspoonful of syrup) two or three times daily, or 5 mg. (one teaspoonful of syrup or one 5 mg. tablet) twice daily, according to body weight. During the first day, the total daily dose should not exceed 10 mg. Dosage is then increased according to the patient's response. (2.5 mg. and 5 mg. suppositories are also available.)

For ages 2 to 6, the total daily dosage usually does not exceed 20 mg. ***For ages 6 to 12,*** the total daily dosage usually does not exceed 25 mg. Because extrapyramidal symptoms have been reported in children as well as in adults, it is important to use the lowest effective dosage.

SIDE EFFECTS

In the dosage range recommended for everyday practice, side effects have been infrequent, transitory and usually mild. A few patients may experience a mild drowsiness when first taking 'Compazine'. There may also be occasional cases of dizziness,

skin reaction and neuromuscular reactions (extrapyramidal symptoms); rarely, hypotension.

Neuromuscular Reactions

Occasionally, neuromuscular reactions (extrapyramidal symptoms) have been observed with 'Compazine' therapy. It is important, therefore, to use the lowest effective dosage, because as dosage is raised the possibility of these reactions increases.

Motor Restlessness: A few patients on 'Compazine'—particularly those in whom dosage has been raised to higher levels—may experience a transient unpleasant stimulation or jitteriness, characterized by restlessness and insomnia. The dosage of 'Compazine' should not be increased while these side effects are present. Patients should be reassured that such effects are temporary and will disappear spontaneously. In those cases where the symptoms are particularly bothersome, reduction of dosage or the concomitant administration of a sedative may be helpful.

Dystonias: These neuromuscular reactions are seen in a significant percentage of hospitalized mental patients on high dosages. The muscles of the face and shoulder girdle may be selectively involved. Symptoms observed have included spasm of the neck muscles, extensor rigidity of back muscles, carpopedal spasm, eyes rolled back, trismus and swallowing difficulty. Despite some similarity to symptoms of serious neurologic disorders, these reactions are usually promptly reversible by temporary discontinuance of 'Compazine' therapy and administration of a sedative such as phenobarbital. The dosage and route of administration should be determined according to the severity of the symptoms. Patients should be reassured that the symptoms are transitory. Depending on the severity of the dystonia, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed. Note: It has been reported that injectable administration of Benadryl* may also be helpful.

Pseudo-parkinsonism: These neuromuscular reactions may resemble the classic parkinsonism syndrome. Treatment should include temporary discontinuance of 'Compazine' therapy and the administration of any standard anti-parkinsonism agent (see *PDR*). Patients should also be reassured that these symptoms are transitory. Depending on the severity of symptoms, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed.

CAUTIONS

Clinical experience has demonstrated that 'Compazine', a phenothiazine derivative, has a wide margin of safety and that there is little likelihood of blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

The antiemetic action of 'Compazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

'Compazine' has no clinically significant potentiating action. However, if depressant agents are used in conjunction with this drug, the possibility of an additive effect should be kept in mind.

CONTRAINDICATIONS

'Compazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

There is a dosage form of 'Compazine' for every medical need. **Tablets,** 5 mg. and 10 mg. and, for use in psychiatry, 25 mg., in bottles of 50, 500 and 5000. Each tablet contains 5 mg., 10 mg., or 25 mg. of prochlorperazine as the dimaleate.

'Spansule' capsules, 10 mg., 15 mg. and 30 mg., in bottles of 30, 250 and 1500; and, for use in psychiatry, 75 mg., in bottles of 30 and 1500. Each capsule contains 10 mg., 15 mg., 30 mg., or 75 mg. of prochlorperazine as the dimaleate.

Ampuls, 2 cc. (5 mg./cc.), in boxes of 6, 100 and 500. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 1 mg. sodium sulfite, 1 mg. sodium bisulfite, 8 mg. sodium phosphate and 12 mg. sodium biphosphate.

Multiple-dose Vials, 10 cc. (5 mg./cc.), in boxes of 1, 20 and 100. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 5 mg. sodium biphosphate, 12 mg. sodium tartrate, 0.9 mg. of sodium saccharin and 0.75% benzyl alcohol as preservative.

Suppositories, 2½ mg. (for young children), 5 mg. (for older children) and 25 mg. (for adults), in boxes of 6. Each suppository contains: 2½ mg., 5 mg., or 25 mg. of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids and lecithin.

Syrup, 5 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. Each 5 cc. contains 5 mg. of prochlorperazine as the ethanedisulfonate.

Concentrate (for hospital use), 10 mg./cc. in 4 fl. oz. bottles, cartons of 12 and 36. Each cc. contains 10 mg. of prochlorperazine as the ethanedisulfonate.

Prescribing information also available in *Compazine® Reference Manual, Physicians' Desk Reference,* or from your SK&F representative or your pharmacist.

Prescribing information adopted January 1961.

STELAZINE®
brand of trifluoperazine

PRESCRIBING INFORMATION

INDICATIONS

In general practice and in psychiatry 'Stelazine' is outstanding among tranquilizers because it relieves anxiety, agitation and tension—without sedation. Nor does it cause euphoria. 'Stelazine' is also effective in relieving anxiety either accompanying or causing somatic conditions. Where anorexia and insomnia are problems, 'Stelazine' usually produces a marked improvement in appetite and sleep patterns.

'Stelazine' provides a fast therapeutic response. On a convenient b.i.d. dosage regimen, many patients who have failed to respond to other agents, or have responded only poorly, are promptly relieved of their symptoms. With symptoms allayed, rapport with the physician is facilitated, and patients are more receptive to counselling or psychotherapy.

In hospitalized psychiatric patients 'Stelazine' produces rapid response in many diagnostic categories. These include acute and chronic schizophrenias, manic-depressive psychoses, involutional psychoses, chronic brain syndrome and mental deficiency.

'Stelazine' can combat psychotic symptoms without causing drowsiness. It can quiet hyperactive patients and activate withdrawn patients, and it has a marked beneficial effect on delusions and hallucinations.

'Stelazine' can rapidly terminate acute psychotic episodes. On the admissions service, intensive 'Stelazine' therapy often results in early discharges.

Also noteworthy is the effectiveness of 'Stelazine' in the treatment of hard-core, chronic and refractory schizophrenics. When administered to a group of such patients, it characteristically produces significant improvement in at least 30% to 40% of them.

ADMINISTRATION AND DOSAGE

Dosage of 'Stelazine' should be adjusted to the needs of the individual.

*Trademark Reg. U.S. Pat. Off.: 'Benadryl' for diphenhydramine hydrochloride, Parke-Davis.

1. Adult Dosage for Use in Everyday Practice

The recommended dosage is 1 mg. or 2 mg. twice daily. In everyday practice, optimal results are usually achieved within this range, so that it is seldom necessary to exceed 4 mg. daily.

Because of the inherent long action of 'Stelazine', patients may be controlled on convenient b.i.d. administration; some patients may be maintained on once-a-day administration.

2. Adult Dosage for Use in Psychiatric Practice

oral (for office patients and outpatients with anxiety): The usual starting dosage is 1 mg. or 2 mg. b.i.d. In the treatment of these patients, it is seldom necessary to exceed 4 mg. a day. (Some patients with more severe disturbances, and discharged mental patients, may require higher dosages.) In some patients, maintenance dosage can be reduced to once-a-day administration.

oral (for patients who are either hospitalized or under adequate supervision): The usual starting dosage is 2 mg. to 5 mg. b.i.d. (Small or emaciated patients should always be started on the lower dosage.)

The majority of patients will show optimum response on 15 mg. or 20 mg. daily, although a few may require 40 mg. a day or more. It is important to give doses that are high enough for long enough periods of time – especially in chronic patients.

Optimum therapeutic dosage levels should be reached within two or three weeks after the start of therapy. When maximum therapeutic response is achieved, dosage may be reduced gradually to a satisfactory maintenance level.

intramuscular (for prompt control of severe symptoms): The usual dosage is 1 mg. to 2 mg. (½-1 cc.) by deep intramuscular injection q4-6h, p.r.n. More than 6 mg. within 24 hours is rarely necessary. As soon as a satisfactory response is observed, oral medication should be substituted at the same dosage level or slightly higher.

Only in very exceptional cases should intramuscular dosage exceed 10 mg. within 24 hours. Since 'Stelazine' has a relatively long duration of action, injections should not be given at intervals of less than 4 hours because of the possibility of an excessive cumulative effect.

'Stelazine' Injection has been exceptionally well tolerated; there is little, if any, pain and irritation at the site of injection.

3. Dosage for Psychotic and Mentally Defective Children

The dosages given below apply to children, ages 6 to 12, who are either hospitalized or under adequate supervision.

oral: The starting dosage is 1 mg. administered once a day or b.i.d., depending on the size of the child. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome. Both the rate and the amount of dosage increases should be carefully adjusted to the size of the child and the severity of the symptoms, and the lowest effective dosage should always be used. Once control is achieved, it is usually possible to reduce dosage to a satisfactory maintenance level.

In most cases, it is not necessary to exceed 15 mg. of 'Stelazine' daily. However, some older children with severe symptoms may require, and be able to tolerate, higher dosages.

intramuscular: There has been little experience with the use of 'Stelazine' Injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg. (½ cc.) of 'Stelazine' may be administered intramuscularly once or twice a day, depending on the size of the child. Once control is achieved, usually after the first day, the oral dosage forms of 'Stelazine' should be substituted for the Injection.

SIDE EFFECTS

In the dosage range of 2-4 mg. daily, side effects from 'Stelazine' are infrequent. When they do occur, they are usually slight and transitory. Mild drowsiness occurs in a small percentage of patients; this usually disappears after a day or two of 'Stelazine' therapy. There are occasional cases of dizziness, mild skin reaction, dry mouth, insomnia and fatigue; rarely, neuromuscular (extrapyramidal) reactions.

In hospitalized psychiatric patients receiving daily 'Stelazine' dosages of 10 mg. or more, clinical experience has shown that, when side effects occur, their appearance is usually restricted to the first two or three weeks of therapy. After this initial period, they appear infrequently, even in the course of prolonged therapy. Termination of 'Stelazine' therapy because of side effects is rarely necessary.

Side effects observed include dizziness, muscular weakness, extrapyramidal symptoms, anorexia, rash, lactation and blurred vision. Drowsiness has occurred, but has been transient, usually disappearing in a day or two.

Neuromuscular (Extrapyramidal) Reactions

These symptoms are seen in a significant number of hospitalized mental patients receiving 'Stelazine'. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

motor restlessness: Some patients may experience an initial transient period of stimulation or jitteriness, chiefly characterized by motor restlessness and sometimes insomnia. These patients should be reassured that this effect is temporary and will disappear spontaneously. The dosage of 'Stelazine' should not be increased while these side effects are present.

If this turbulent phase becomes too troublesome, the symptoms can be controlled by a reduction of dosage or the concomitant administration of a barbiturate.

dystonias: These symptoms are rare outside of mental hospitals, but they may be observed occasionally in patients who have received 'Stelazine' as a mild tranquilizer.

Symptoms may include: spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

The onset of the dystonias may be sudden. A primary characteristic of these symptoms is their intermittency. They may last several minutes, disappear and then recur. There is typically no loss of consciousness and definite prodromata are usually present. Initially, these intermittent symptoms occur in a crescendo of intensity. Then as the effect of the drug wears off, the intervals between the occurrence of symptoms become longer, and the intensity of the symptoms subsides.

Despite their similarity to symptoms of serious neurological disorders, these dystonias are usually promptly reversible and need not cause undue alarm. They usually subside gradually within a few hours, and almost always within 24 to 48 hours, after the drug has been temporarily discontinued. If 'Stelazine' therapy is discontinued, it should be reinstituted at a lower dosage.

Treatment is symptomatic and conservative. *In mild cases,* reassurance of the patient is often sufficient therapy. Barbiturates are also useful. *In moderate cases,* barbiturates will usually bring rapid relief. The dosage and route of administration of the barbiturate used should be determined by the intensity of the symptoms and the response of the patient. *In more severe adult cases,* the administration of an anti-parkinsonism agent (see *Physicians' Desk Reference*) produces rapid, often dramatic, reversal of symptoms. Also, intravenous caffeine and sodium benzoate seems to be an effective and rapid antagonist to the dystonias. Depending on the severity of the dystonia, suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed. *In children,* reassurance and barbiturates will usually control symptoms. Dosage and route of administration should be determined according to the intensity of symptoms and response of patient.

Note: It has been reported that injectable administration of 'Benadryl' may also be helpful in controlling dystonias.

pseudo-parkinsonism: These symptoms are extremely rare outside of mental hospitals.

Symptoms include: mask-like facies; drooling; tremors; pill-rolling motion; and shuffling gait.

Reassurance and sedation are important components of effective therapy. In the majority of cases these symptoms are readily reversible when an anti-parkinsonism agent is administered concomitantly with 'Stelazine'. Occasionally it is necessary to lower the dosage or to temporarily discontinue the drug. Depending on the severity of symptoms, suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed. If 'Stelazine' therapy is discontinued, it should be reinstituted at a lower dosage.

CAUTIONS

Clinical experience has demonstrated that 'Stelazine', a phenothiazine derivative, has a wide range of safety and that there is little likelihood of either blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

One of the results of 'Stelazine' therapy may be an increase in mental and physical activity. In some patients, this effect may not be desired. For example, although 'Stelazine' has relieved anxiety and, at the same time, anginal pain in patients with angina pectoris, a few such patients have complained of increased pain while taking 'Stelazine'. Therefore, if 'Stelazine' is used in angina patients, they should be observed carefully and, if an unfavorable response is noted, the drug should be withdrawn.

Hypotension has not been a problem, but nevertheless adequate precautions should be taken when the drug is used in patients with impaired cardiovascular systems.

The antiemetic action of 'Stelazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

Although 'Stelazine' has shown very little potentiating activity, caution should be observed when it is used in large doses in conjunction with sedatives or depressants.

CONTRAINDICATIONS

'Stelazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

Tablets, 1 mg. and 2 mg., in bottles of 50, 500 and 5000. (Each tablet contains 1 mg. or 2 mg. of trifluoperazine as the dihydrochloride.)

For psychiatric patients who are hospitalized or under close supervision:

Tablets, 5 mg. and 10 mg., in bottles of 50, 1500 and 5000. (Each tablet contains 5 mg. or 10 mg. of trifluoperazine as the dihydrochloride.)

Multiple-dose Vials, 10 cc. (2 mg./cc.), in boxes of 1 and 20. (Each cc. contains, in aqueous solution, 2 mg. of trifluoperazine as the dihydrochloride, 4.75 mg. of sodium tartrate, 11.6 mg. of sodium biphosphate, 0.3 mg. of sodium saccharin, and 0.75% of benzyl alcohol as preservative.)

Concentrate (for hospital use), 10 mg./cc., in 2 fl. oz. bottles, in cartons of 4 and 12. (Each cc. contains 10 mg. of trifluoperazine as the dihydrochloride.)

Prescribing information adopted July 1961

PARNATE®

brand of tranylcypromine

PRESCRIBING INFORMATION

The physician should be familiar with the material on dosage, side effects and cautions given below before prescribing 'Parnate', and with the principles of monoamine oxidase inhibitor therapy and the side effects of this class of drugs as reported in the literature. Also, the physician should be familiar with the symptomatology of mental depressions and alternative methods of treatment to aid in the careful selection of patients for 'Parnate' therapy.

INDICATIONS AND LIMITATIONS OF USE

'Parnate' is indicated for the relief of symptoms of mental depression which may include dejected mood, self-depreciation, lowered activity levels, difficulty in making decisions, disturbed eating and sleeping patterns, and variations of these basic symptoms as described in the literature. The therapeutic utility of monoamine oxidase inhibitors is limited specifically to depressive symptoms; these drugs may aggravate some co-existing symptoms such as agitation or anxiety.

In psychiatry, 'Parnate' is indicated in the following diagnostic categories, subject to the limitation stated above: reactive and other psychoneurotic depressions, involutional melancholia, depressive phase of manic-depressive psychosis, psychotic depressive reactions. In the psychiatric treatment of severe endogenous depressions, it is impossible to predict, with presently known data, which patients will respond best to 'Parnate' and which to ECT. 'Parnate' may be indicated in some reactive depressions in which ECT is not indicated. 'Parnate' is not recommended to treat essentially normal responses to temporary situational difficulties.

Note: In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety and agitation. Also, of course, some patients fail to respond to drug therapy.

CLINICAL EXPERIENCE

Extensive clinical trials with 'Parnate' have confirmed its effectiveness and versatility. As always in the evaluation of drugs for psychic disorders, some variation in efficacy has been reported.

These studies provide the following data on the effectiveness and fundamental properties of 'Parnate':

1. In 500 patients on whom complete data are available for statistical analysis, marked or moderate improvement was reported in 77% of the nonpsychotic patients. Marked improvement was reported in 40% and moderate improvement in 27% of the psychotic patients. Some investigators have pointed out that improvement in certain instances, particularly in milder cases, may have been due to spontaneous remission of symptoms.
2. Improvement is seen within 48 hours to three weeks after starting 'Parnate'; the response can be accelerated by using higher than standard initial dosages.
3. 'Parnate' acts primarily as an antidepressant rather than as a euphoriant. Patients feel essentially normal on 'Parnate' therapy.
4. 'Parnate' can facilitate psychotherapy by increasing the patient's willingness to exert mental effort and reducing symptom-centered preoccupations.
5. 'Parnate' appears to prevent relapses in some patients who have been treated initially with ECT.

DOSAGE

Dosage should be adjusted to the requirements of the individual patient. Dosage increases should be made only in increments of 10 mg. per day and ordinarily at intervals of one to three weeks. Side effects occur more often as dosage is increased.

Reduction from peak to maintenance dosage may be desirable before withdrawal. If withdrawn prematurely, original symptoms will recur. No tendency to produce rebound depressions of greater intensity has been seen with 'Parnate', although this is a theoretical possibility in patients treated at high dosages. Experimental work indicates that inhibition of monoamine

oxidase persists for only a few days after withdrawal. Thus, any side effects due to this inhibition will probably recede rapidly upon withdrawal, which should be a distinct advantage of 'Parnate' therapy when the patient exhibits poor tolerance to antidepressant medication.

Because there is a striking relationship between dosage and speed of response, two dosage schedules are provided:

A. Standard dosage. (This schedule will not always produce prompt results, but it will hold the incidence of side effects to a minimum.)

1. Recommended starting dosage is 20 mg. per day — administered 10 mg. b.i.d. (morning and afternoon).
2. Continue this dosage for two to three weeks.
3. If no signs of a response appear, increase dosage to 30 mg. daily—20 mg. upon arising and 10 mg. in the afternoon.
4. Continue this dosage for at least a week.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced to a maintenance level.
6. Some patients will be maintained on 20 mg. per day; many will need only 10 mg. daily.
7. If dosages above 30 mg. daily are desired for use in exceptionally resistant cases, refer to the schedule of intensive dosage.

B. Intensive dosage (for accelerated response). (This schedule is for use in hospitalized patients or those under comparable supervision whenever a prompt effect is more desirable than a relative absence of side effects.)

1. Recommended starting dosage is 30 mg. per day. Administer 20 mg. in the morning and 10 mg. in the afternoon.
2. Continue this dosage for one week.
3. If no signs of a response appear, increase dosage gradually at intervals of several days to one week.
4. Dosages above 60 mg. per day are not advisable.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced gradually to a maintenance level.
6. Some patients may be maintained on 20 mg. per day; many will need only 10 mg. daily.

Note: When ECT is being administered concurrently, 10 mg. b.i.d. can usually be given during the series, then reduced to 10 mg. daily for maintenance therapy.

SIDE EFFECTS

A. At standard dosages. Side effects in patients treated with standard doses of 'Parnate' are qualitatively the same as seen at higher dosages but are generally less frequent and less severe.

The patient may experience restlessness, overstimulation, or insomnia; may notice some weakness, drowsiness, episodes of dizziness, or dry mouth; or may report nausea, diarrhea, abdominal pain, or constipation. Occasionally, headaches have occurred. Symptoms of postural hypotension have been seen most commonly, but not exclusively, in patients with pre-existent hypertension; blood pressure returns to pretreatment levels rapidly upon discontinuation of the drug. Other side effects which might occur in rare instances are tachycardia, urinary retention, significant anorexia, skin rashes, edema, palpitations, blurred vision, tinnitus, chills, paresthesia, muscle spasm and tremors, impotence, sweating and possibly paradoxical hypertension.

Most of these side effects can usually be relieved by lowering the dosage or by giving suitable concomitant medication.

B. At intensive treatment dosages. When 'Parnate' is used for intensive treatment to control symptoms more rapidly, an increase in the incidence and severity of side effects must be anticipated.

At doses above 30 mg. daily, postural hypotension is a major side effect of 'Parnate' therapy. It affects largely the systolic readings and occurs mainly, but not exclusively, in patients with a history of hypertension. Rare instances of syncope have been seen. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the starting dose. Postural hypotension can be relieved by having the patient lie down until blood pressure returns to normal.

Other side effects which may occur are listed above under *standard dosages*. Headaches have occasionally been severe and incapacitating. Overstimulated behavior, which may include increased anxiety, agitation and manic symptoms, can be evidence of either a side effect or an excessive therapeutic action; if this occurs, reduce dosage or administer a phenothiazine tranquilizer.

CAUTIONS

Extensive clinical and laboratory work has shown that there is little likelihood of blood or liver toxicity. Since 'Parnate' is a non-hydrazine compound, it should prove to be exempt from the toxic effects on the liver thought to be due to the hydrazine moiety of some other drugs. However, severe toxic reactions have occurred with some monoamine oxidase inhibitors. Pending further clinical experience, 'Parnate' should probably not be used in patients with a history of liver disease or in those with abnormal liver function tests. Drug-induced jaundice is often difficult to differentiate from other jaundice. However, there has been sufficient clinical experience with 'Parnate' to demonstrate that, if it has any potentiality for producing jaundice, the reaction must be rare. Also, the usual precautions should be observed in patients with impaired renal function since there is a possibility of accumulative effects in such patients.

Although 'Parnate' has been used in combination with various drugs (particularly Stelazine®, brand of trifluoperazine), some monoamine oxidase inhibitors have been reported to have marked potentiating effects on certain drugs, e.g., sympathomimetics, central nervous system depressants, hypotensive agents and alcohol. Therefore, the physician should bear in mind the possibility of a lowered margin of safety when 'Parnate' is combined with potent drugs and should adjust dosage carefully. 'Parnate' should not be used in combination with imipramine. (The reaction of a patient who attempted suicide with a deliberate overdosage of 'Parnate' and imipramine was more severe than would have been predicted from the properties of either drug.)

CASES REQUIRING SPECIAL CONSIDERATION

Administer with caution to patients with recent myocardial infarction or coronary artery disease with angina of effort. Increased physical activity and, more rarely, hypotension have been reported. The pharmacologic properties of 'Parnate' suggest that it may have a capacity to suppress anginal pain that would otherwise serve as a warning sign of myocardial ischemia. When 'Parnate', like any agent which lowers blood pressure, is withdrawn from patients who tend to be hypertensive, blood pressure may again rise to undesirable levels.

When 'Parnate' is combined with a phenothiazine derivative or other compound known to affect blood pressure, elderly patients and those with cardiovascular inadequacies should be observed more closely because of the possibility of additive hypotensive effects.

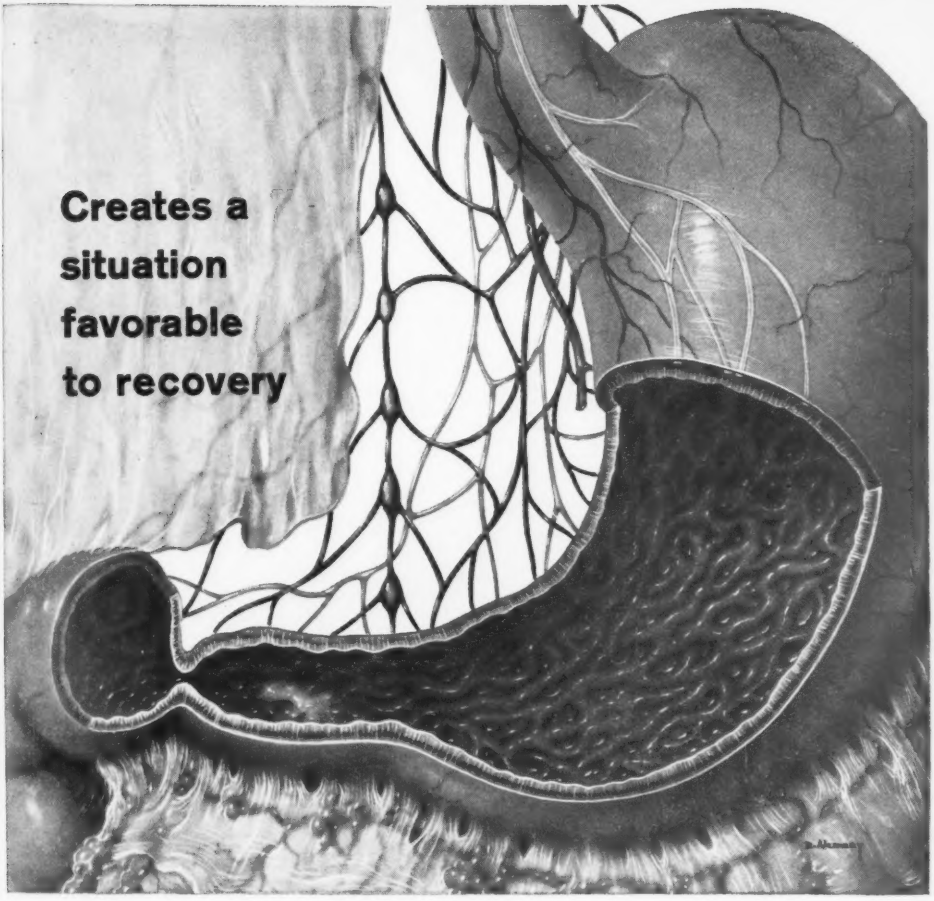
In patients being transferred to 'Parnate' from another monoamine oxidase inhibitor or from imipramine, allow a medication-free interval of one week, then initiate 'Parnate' using half the normal dosage for at least the first week of therapy. Similarly, a few days should elapse between the discontinuance of 'Parnate' and the administration of another monoamine oxidase inhibitor or of imipramine.

Because the influence of 'Parnate' on the convulsive threshold is variable in animal experiments, suitable precautions should be taken if epileptic patients are treated.

AVAILABLE

Tablets, 10 mg., in bottles of 50 and 1500. (Each tablet contains 10 mg. of tranylcypromine, as the sulfate.)

Prescribing information adopted Feb. 1961.



In Pylorospasm: 'Combid' *Spansule* capsules provide relief of psychic as well as physical factors. The anxiety, tension and apprehension that cause or complicate pyloroduodenal irritability are controlled. At the same time, the spasm itself is reduced.

'Combid' relieves irritability and hypermotility for 10 to 12 hours (all day or all night) after one dose.

SK&F

Combid® Spansule®

brand of sustained release capsules

'Combid' *Spansule* capsules are a logical combination of 5 mg. of Darbid® (brand of isopropamide) as the iodide, a unique, inherently long-acting anticholinergic; and 10 mg. of Compazine® (brand of prochlorperazine) as the dimaleate, the outstanding tranquilizer/antiemetic in sustained release form.

Among the many conditions in which 'Combid' *Spansule* capsules are indicated are: peptic ulcer, hyperchlorhydria, pyloroduodenal irritability, irritable or spastic colon, gastric neurosis, gastritis, aerophagia, pyrosis, "nervous stomach," functional diarrhea, drug-induced diarrhea, mucous colitis, ulcerative colitis, genitourinary spasm, and nausea and vomiting of pregnancy.

DOSAGE: One 'Combid' *Spansule* capsule b.i.d. (every 12 hours). Some patients may require only one capsule every 24 hours, on arising. Only in the exceptional patient will it be necessary to increase the dosage to two capsules b.i.d. (morning and evening).

CAUTIONS AND CONTRAINDICATIONS: As is true with any preparation containing an anticholinergic, 'Combid' *Spansule* capsules should not be prescribed for patients with glaucoma, pyloric obstruction, or prostatic hypertrophy. Also, because of the antiemetic action of the 'Compazine' component (a phenothiazine derivative), 'Combid' *Spansule* capsules should not be used where nausea and vomiting are believed to be a manifestation of intestinal obstruction or brain tumor.

Clinical experience has demonstrated that 'Combid' has a wide margin of safety and that there is little likelihood of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence. When 'Combid' is used with depressant drugs, the possibility of an additive effect should be borne in mind. An occasional patient may experience mild drowsiness when first taking 'Combid'.

Prescribing information adopted January, 1961.

In hay fever and other seasonal allergies . . .

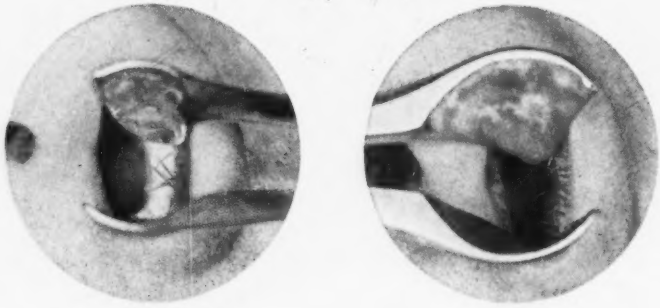
ORNADE® SPANSULE®

brand of sustained release capsules

the unique oral nasal decongestant with a special drying agent

relieves sneezing—weeping—nasal congestion

for 24 hours with just two doses daily



Before taking 'Ornade' — 2 hours after taking 'Ornade'

PRESCRIBING INFORMATION

The comprehensive formula of 'Ornade' *Spansule* capsules contains a special drying agent, isopropamide iodide, in addition to a decongestant and an antihistamine. Isopropamide iodide acts to reduce excessive weeping and nasal and paranasal secretions. The decongestant, phenylpropanolamine, reduces vascular engorgement and often permits blocked sinus cavities to drain. The antihistamine, 'Teldrin', reduces sneezing, rhinorrhea and itching of the eyes. Acting together, additively, these three agents combine to provide outstanding relief from upper respiratory distress.

INDICATIONS: 'Ornade' *Spansule* capsules are recommended for prompt and prolonged relief from respiratory tract congestion and hypersecretion associated with:

- allergic rhinitis:
  - hay fever
  - "rose fever," etc.
- the common cold
- acute, subacute and chronic sinusitis
- influenza
- vasomotor rhinitis
- postnasal drip

DOSAGE (adults and children over 6): For all-day, all-night relief, one 'Ornade' *Spansule* capsule q12h. When taken at bedtime, 'Ornade' keeps patients symptom-free throughout the night and usually enables them to wake up in the morning uncongested and with airways free.

FORMULA: Each 'Ornade' *Spansule* sustained release capsule contains 8 mg. of Teldrin® (brand of chlorpheniramine maleate) and 50 mg. of phenylpropanolamine hydrochloride, so prepared that a therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours; and 2.5 mg. of isopropamide, as the iodide. Because isopropamide iodide is inherently long-acting, it has not been necessary to put it into sustained release form; therefore, the entire dose of isopropamide iodide is released upon ingestion.

SIDE EFFECTS: Drowsiness, "nervousness," or insomnia may occur on rare occasions, but are usually mild and transitory.

CAUTIONS AND CONTRAINDICATIONS: Use with caution in the presence of severe hypertension. 'Ornade' should not be used in patients with glaucoma or prostatic hypertrophy.

AVAILABLE: 'Ornade' *Spansule* capsules are available in bottles of 30 and 250.

Prescribing information adopted January, 1961.

Smith Kline & French Laboratories

SK&F